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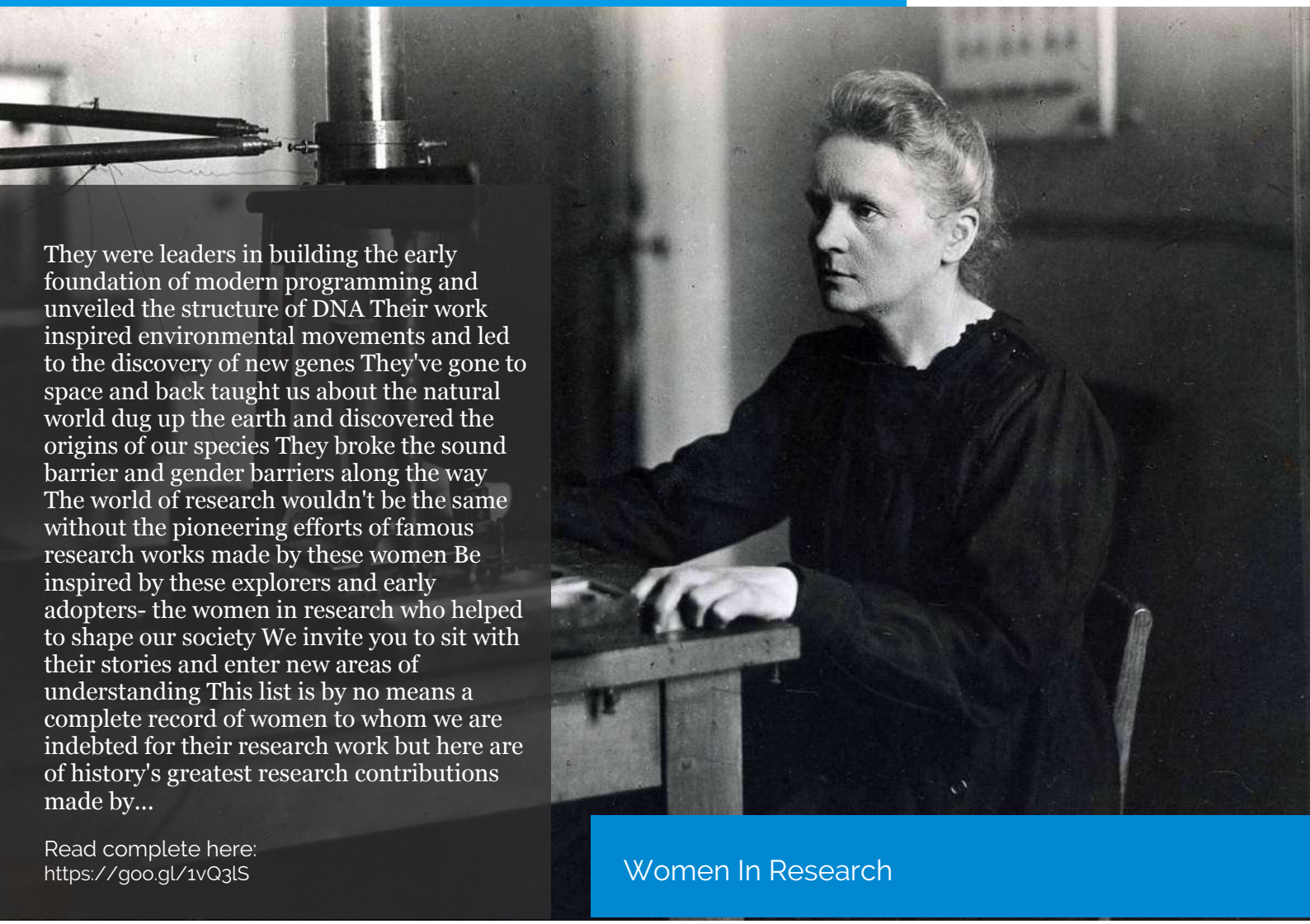

They were leaders in building the early foundation of modern programming and unveiled the structure of DNA Their work inspired environmental movements and led to the discovery of new genes They've gone to space and back taught us about the natural world dug up the earth and discovered the origins of our species They broke the sound barrier and gender barriers along the way The world of research wouldn't be the same without the pioneering efforts of famous research works made by these women Be inspired by these explorers and early adopters- the women in research who helped to shape our society We invite you to sit with their stories and enter new areas of understanding This list is by no means a complete record of women to whom we are indebted for their research work but here are of history's greatest research contributions made by...

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Prevalence and Factors Associated with COVID-19 Vaccine Acceptance among Adult Population in Northern Uganda. A Cross-Sectional Study

Pamela Atim, Nelson Onira Alema, Denis Acullu, Johnson Nyeko Oloya, Steven Baguma, Christopher Okot, Denis Ochula, Patrick Odong Olwedo, Smart Godfrey Okot, Francis Pebalo Pebolo, Freddy Wathum Drinkwater Oyat, Eric Nzirakaindi Ikoona, Judith Aloyo & David Lagoro Kitara

Gulu University

ABSTRACT

Background: When COVID-19 vaccines arrived in Uganda in March of 2021, there was inadequate information on vaccine acceptance in the population due to many factors, but mainly due to misinformation and disinformation circulating in Ugandan media. This study aimed to determine the prevalence and factors associated with COVID-19 vaccine acceptance among adult population in northern Uganda.

Methods: We conducted a cross-sectional study on 723-adult populations in northern Uganda from March to April of 2022. Participants were selected by systematic sampling from twenty- four health facilities in Acholi sub-region. SPSS version 25.0 was used for data analysis at multivariable regression analysis and a p-value <0.05 was considered significant.

Keywords: COVID-19 vaccine, acceptance, prevalence, Village health teams (VHTs).

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Pamela Atim[α], Nelson Onira Alema[σ], Denis Acullu[ρ], Johnson Nyeko Oloya[ↀ], Steven Baguma [¥], Christopher Okot[§], Denis Ochula[χ], Patrick Odong Olwedo[ν], Smart Godfrey Okot[Θ], Francis Pebalo Pebolo[ζ], Freddy Wathum Drinkwater Oyat[£], Eric Nzirakaindi Ikoona[€], Judith Aloyo[₣] & David Lagoro Kitara[₴]

ABSTRACT

Background: When COVID-19 vaccines arrived in Uganda in March of 2021, there was inadequate information on vaccine acceptance in the population due to many factors, but mainly due to misinformation and disinformation circulating in Ugandan media. This study aimed to determine the prevalence and factors associated with COVID-19 vaccine acceptance among adult population in northern Uganda.

Methods: We conducted a cross-sectional study on 723-adult populations in northern Uganda from March to April of 2022. Participants were selected by systematic sampling from twenty-four health facilities in Acholi sub-region. SPSS version 25.0 was used for data analysis at multivariable regression analysis and a p-value <0.05 was considered significant.

Results: COVID-19 vaccine acceptance among adult population (mean age, 31.36 years SD±10.07), (95% CI:30.62-32.10) was high at 580/723 (80.2%, 95%CI: 78.9%-83.4%). Factors associated with vaccine acceptance were likely among participants who strongly disagree (aOR=adjusted Odds Ratio), aOR=3.31,95% CI:1.49-7.36; p=0.003) and disagree (aOR=1.98, 95%CI:1.01-3.89; p=0.046) that vaccines in health facilities in northern Uganda were safe than those who strongly agree, respectively; participants from Gulu (aOR=5.19,95%CI:1.71 -15.80; p=0.004), Kitgum (aOR=6.05,95%CI: 1.76-20.80; p=0.004), and Pader districts (aOR=3.45,95%CI:1.07-11.14; p=0.038) than Lamwo district, respectively; smokers (aOR= 7.75,95%CI:2.06-29.23; p=0.002) than non-smokers; non-health workers (aOR=1.74,95% CI:1.03-2.96; p=0.040) than health workers; females (aOR=1.59,95%CI:1.04-2.42; p=0.032) than males; Baganda tribe (aOR=5.19,95% CI:1.71-15.80;p=0.004); and other tribes (aOR= 6.05,95%CI:1.76-20.80; p=0.040) than Itesot, respectively. However, it was less likely for participants with comorbidities (aOR=0.42,95% CI:0.25-0.71; p=0.001); graduates (aOR=0.42, 95%CI:0.18-0.99; p=0.049); and age-group of 20-29 years (aOR=0.52,95%CI:0.31-2.96; p=0. 040) to accept COVID-19 vaccines.

Conclusion: COVID-19 vaccine acceptance among participants from northern Uganda was high. Participants who strongly disagree and disagree that vaccines in northern Uganda's health facilities were safe; smokers, non-health workers, females, Baganda tribe, and participants from Gulu, Kitgum, and Pader districts were more likely to accept COVID-19 vaccines. However, it was less likely for participants with comorbidities, age-group of 20-29 years, and graduates to accept COVID-19 vaccines. The fear of contracting coronavirus and death if not vaccinated contributed substantially to COVID-19 vaccine acceptance.

There is a need to engage, sensitize and mobilize the population on COVID-19 vaccines using community health workers such as the village health teams (VHTs).

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Keywords: COVID-19 vaccine, acceptance, prevalence, Village health teams (VHTs).

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I. INTRODUCTION

Coronavirus disease 2019 (COVID-19) is one of today's most significant public health worries world-wide [1,2]. As a result, much effort has been devoted to implementing control strategies for COVID-19 pandemic globally, for example, lockdown measures, travel bans, isolation of confirmed cases and close contacts, bans on mass gatherings, social distancing, wearing facemasks, COVID-19 vaccination, and other hygiene measures, but the transmission of the virus is likely to blowback when these strategies are lifted [2]. Thus, many scholars, academicians, physicians, and public health specialists have observed that of the many approaches to control this pandemic, mass COVID-19 vaccination is one of the top priority interventions [3]. It is now known that COVID-19 vaccines can potentially decrease the spread of coronavirus by reducing its incidence, risks of developing severe disease and hospitalization, and death in the general population; however, these have generated a lot of debate in the population [4].

Reports from Vaccine Alliance found that wealthier nations had hoarded so much of COVID-19 vaccines that it was predicted that many of the low-to-middle-income countries would most likely not receive COVID-19 vaccines in 2021 [5]. In addition, in Africa, where most vaccines for many killer diseases have been very successful in reducing infant and child mortality rates and increased the lifespan of the current population, the population suffered from false rumors and conspiracy theories that have led to COVID-19 vaccine hesitancy; a factor jeopardizing critical efforts to stop the spread of severe -acute-respiratory-syndrome-coronavirus-2 (SAR S-CoV-2) on the continent [5].

Also, vaccine safety and access to COVID-19 vaccines have been among the top concerns of most respondents in a survey conducted by GeoPoll in sub-Saharan Africa [5]. The survey showed that 23% of respondents believed that whoever paid for COVID-19 vaccines got it first, thus highlighting the inequity in healthcare resource distribution at critical moments, especially in sub-Saharan Africa [5].

Experts have described COVID-19 vaccine hesitancy as one of the top ten commonest threats to global health security in 2019 [6], and as defined by the World Health Organization (WHO), vaccine hesitancy is a reluctance or refusal by a person to get vaccinated despite availability of vaccines [6]. Accordingly, WHO states that some reasons people choose not to get vaccinated include the lack of trust in the healthcare systems, complacency, and inconvenience in getting vaccines [6]. On the other hand, vaccine acceptance is defined as the degree to which individuals accept, question, or refuse vaccination, and it determines vaccine uptake and distribution successes [7].

As part of a broader process to prioritize frontline health workers' vaccination with limited COVID-19 vaccines in Uganda, a recent report from Amuru district local government in northern

Uganda showed that most COVID-19 vaccines sent for health workers were not used and were at risk of getting expired [7]. In response, the Resident District Commissioner (RDC) of Amuru issued an ultimatum to health workers to either get vaccinated with COVID-19 vaccines or quit their jobs [8].

So, looking broadly at vaccine acceptance in Uganda, it was found that approximately 60% (600/1,000) of respondents were interested in getting COVID-19 vaccines [9]. However, there were no comprehensive details on regional prevalence of COVID-19 vaccine acceptance as Uganda prepared to roll out mass COVID-19 vaccinations. As seen in many reports on the management of diseases with epidemic potential, population's education is part of the prevention and control strategies, particularly to inform people to change their habits and behaviors and holistically tackle the spread of the infection [10].

However, despite this vast knowledge on the role played by the population's goodwill in managing epidemics, some African governments still wanted to cut health education-related budgets during the COVID-19 pandemic [10]. Such moves on health budget cuts during the pandemic could hamper efforts to effectively educate and vaccinate the general population in the African continent.

Remarkably, one study conducted among medical students in the United States of America (USA) showed that there was COVID-19 vaccine hesitancy and that 23% were unwilling to take COVID-19 vaccines [11]. Students raised concerns about COVID-19 vaccines, especially regarding the population's trust in public healthcare systems and side effects of COVID-19 vaccines [11].

Similarly, findings among university students in Italy, the United Kingdom, and Turkey showed a high COVID-19 vaccine hesitancy ranging from 14% to 31% [12].

On COVID-19 vaccine hesitancy, many scholars and experts view the many uncertainties surrounding the origin of the SAR-CoV-2 virus as the main underlying reason [13]. In addition, a study found that COVID-19 vaccine hesitancy was associated with beliefs and suspicions about the origin of the SAR-CoV-2 virus [13]. It is said that most people who believed in the natural evolution of SAR-CoV-2 virus were more likely to accept COVID-19 vaccines than those who thought the virus was manufactured [13].

In Jordan and Kuwait, a study investigating COVID-19 vaccine hesitancy found that misinformation and disinformation circulating in social media with numerous conspiracy theories extensively played a part in vaccine hesitancy in that population [14]. In the same study, 28% of participants believed COVID-19 vaccines were to introduce microchips into recipients' bodies, and 23% thought COVID-19 vaccines were to reduce fertility in their population [14].

Also, a study on COVID-19 vaccine hesitancy in healthcare workers in two large academic centers in South Africa found that 90% of the 1308 sampled population accepted COVID-19 vaccines [15]. However, healthcare workers with lower educational status and those who previously refused other vaccines were less likely to take COVID-19 vaccines [15]. In addition, Ahmed and colleagues researching COVID-19 vaccine acceptability in Somalia found that 23% of their survey population were reluctant to take COVID-19 vaccines, and being a female was associated with vaccine hesitancy [16].

Not much is known or published on COVID-19 vaccine acceptance in the general Ugandan population. Because of this, several questions have been raised, and many more unanswered questions are being asked on the level of vaccine hesitancy/inquisitiveness or acceptance in the general Ugandan population as the country prepared to roll out COVID-19 vaccinations.

This study aimed to determine the prevalence and factors associated with COVID-19 vaccine acceptance among adult population of northern Uganda.

II. METHODS

Study design: We conducted a cross-sectional study among adult population in northern Uganda from March to April 2022.

2.1 Study Sites

The study was conducted in Outpatient Departments (OPDs) of twenty-four health facilities in nine districts of Acholi sub- region in northern Uganda. Namukora HC IV, Kitgum Government, and St. Joseph's Hospitals in Kitgum district; Padibe HC IV, Palabek HC III, and Madi Open HC IV in Lamwo district; Pajule HC IV, Atanga-Lacekocot HCIII and Pader HC III in Pader district, Dr. Ambrosoli memorial Hospital, Kalongo and Patongo HCIII in Agago district; Lalogi HC IV, Opit HC III and Odek HC III in Omoro district; Anaka Hospital and Koch Goma HC III in Nwoya district; Atiak HC IV, Pabbo HCIII and Amuru HC III in Amuru district, St. Mary's Hospital Lacor, Independent Hospital, Gulu Regional Referral Hospital in Gulu City; Awach HC IV and Cwero HC III in Gulu district.

These health centers (HCs) were selected based on their participation in offering free COVID-19 vaccines to the region's population.

2.2 Study Population

We recruited participants (adults/≥18 years) who were attendees or attendants to outpatient clinics of the twenty-four health facilities in northern Uganda's nine districts of the Acholi sub-region.

2.3 Selection Criteria

The selection of participants was stratified at regional level into nine districts of the Acholi subregion and at district level to twenty-four health facilities (Hospitals, HCIVs, and HCIIIs).

The study was conducted in the Outpatient Department (OPD) in each of the twenty-four health facilities. Participants were selected by systematic sampling in that every third adult attendee or attendant aged 18 years and above who consented to the study were recruited. We excluded participants who were critically ill and those who were not willing to answer our research questions.

2.4 Sample Size Estimation

The sample size was calculated based on the Raosoft sample size calculation methods. The computation was built on a 50% response distribution, 5% margin of error, and 95% Confidence Interval. The online software foundation uses a widely utilized descriptive sample size estimation formula [17,18]. The research team chose this software calculator because Raosoft, Inc. form and survey software comprises a database management system of great strength and reliability that communicates with other proprietary formats. In addition, the Raosoft database is a highly robust, proven system with high data integrity and security [17,18].

$$\text{The sample size was calculated using the formula} = \frac{(\text{z-score})^2 \times \text{StdDev} \times (1-\text{StdDev})}{(\text{Confidence Interval})^2}$$

Based on the assumption of a population size of 45,000 clients and visitors in one month in all the health facilities in the Acholi subregion, the minimum sample size was calculated to be 396 participants.

2.5 Sampling Technique

We conducted a stratified sampling approach at regional and district levels, and a systematic sampling approach for selecting participants at each of the twenty-four health facility's outpatient departments [19]. The Acholi subregion was stratified into the nine districts (Gulu City, Gulu, Nwoya, Amuru, Omoro, Pader, Agago, Kitgum, and Lamwo districts) and further into twenty-four selected health facilities (Hospitals, HCIVs, and HCIIIs) where COVID-19 vaccines were administered freely to the population. At each outpatient department, every day from morning to evening, a third attendee or attendant was selected from the OPD register by a systematic sampling method for one week until the required sample size was achieved [19,20].

It was estimated that approximately 45,000 people receive health services in the twenty-four selected health facilities' outpatient departments in one month. We also defined systematic sampling as a probability sampling method where researchers select population members at regular intervals [19, 20]. We chose this sampling

technique because it allowed us to quickly get the desired sample size, thereby reducing the risk of our study team acquiring COVID-19. In addition, we chose the outpatients' department because it was the most convenient place to receive participants for this study as most population were still apprehensive about receiving or accepting visitors or researchers in their homes, offices, or public places as the Government of Uganda had recently eased the lockdown measures and the population were still in fear of contracting the virus.

Also, outpatient departments had the required facilities for infection, prevention, and control (IPC) and standard operating procedures (SOPs), allowing interviewees and interviewers to interact while following the national COVID-19 standard protocols. Last but most importantly, systematic sampling method helps to minimize biased samples and poor survey results in addition to eliminating clustered selection with a low probability of obtaining contaminated data [19, 20], which was the ideal situation the research team had to achieve.

2.6 Study Variables

The dependent variable was COVID-19 vaccine acceptance ("Have you received a jab of COVID-19 vaccine? and the answer was either "yes" and coded as "1" or "no" and coded as "0" for the analysis).

The independent variables were the sociodemographic characteristics such as; age, sex, occupation, religion, level of education, tribe, marital status, districts, presence of comorbidities, nationality, race, health insurance coverage status, and whether participants "Strongly agree" ("SA"), "Agree," ("A"), "Neutral" ("N"), "Disagree" ("DA") or "Strongly Disagree," ("SD") that vaccines in health facilities in northern Uganda were safe.

2.7 Data Collection Methods

Data were collected using face-to-face questionnaire interviews by our research team, strictly following Uganda's standard operating procedures (SOPs) and COVID-19 infection, prevention, and control (IPC) guidelines [21]. We used a questionnaire constructed in English, consisting of questions on sociodemographic characteristics and participants' views on vaccine safety in health facilities in the Acholi sub-region *(Additional file 1)*. The questionnaire was developed and grounded on literature reviews and discussions by our research team [22, 23].

Further, the questionnaire was pretested among out patients at Gulu Regional Referral Hospital with an internal validity of Cronbach's α=0.772.

Also, participants were assured of confidentiality and privacy of their responses to reduce potential bias introduced by self-reported data. In addition, the questionnaire was designed short to minimize lethargy in answering questions which made it easy for participants' responses.

2.8 Data Analysis

Data analysis was performed using SPSS statistical software version 25.0. Continuous variables were presented in means, histograms, standard deviations, medians, and interquartile ranges. Categorical data were presented as frequencies and percentages. Chi-square and crosstabs tests were performed on categorical data when comparing two or more groups. Also, to assess associations of each independent variable with COVID-19 vaccine acceptance (dependent variable), a bivariable logistic regression analysis was conducted and Crude Odds Ratios (COR), at 95% Confidence Intervals (CI) and P-values were presented.

Independent variables found insignificant at bivariable level but with (P-values ⩽0.20) were included in the final multivariable logistic regression analysis model together with significant independent variables and the dependent variable. However, independent variables that had P-values above 0.201 at bivariable level were not included in the final multivariable regression models. In the multivariable regression analysis, we constructed two models by categorizing independent variables into sociodemographic characteristics, comorbidity status, national insurance coverage status, and participants' views on safety of vaccines in health facilities of northern Uganda.

The first multivariable logistic regression model included participant's socio-demographic characteristics (age, sex, level of education, districts, religion, occupation, and smoking status). After that, we constructed a second and final multivariable regression model adjusting for participants' comorbidity status, health insurance coverage status and views on the safety of vaccines in health facilities of northern Uganda.

The adjusted odds ratios (aOR) at 95% Confidence Intervals (CI) and p-values were determined with a significant level set at a p-value <0.05.

2.9 Ethical Approval

This study was approved by St. Mary's Hospital, Lacor Institutional, Review and Ethics Committee (LHIREC No. 0193/10/2021) and administrative clearance from the twenty-four health facilities. In addition, each participant consented before being recruited to the study. The research team ensured that confidentiality of personal information was maintained during the investigation, and only participants' unique identifiers were retained on public records. During the study, only the Principal Investigator and supervisors accessed participants' database and at the end of the project, the database was archived at Gulu University, Faculty of Medicine, in the Department of Surgery.

IIII. RESULTS

The most important finding from this study was that COVID-19 vaccine acceptance among adult participants in northern Uganda was high at 580/723 (80.2%, 95%CI: 78.9%-83.4%). Among sociodemographic characteristics, most participants were males 394/723 (54.5%), in the age-group of 20-29 years 279/723 (38.6%) and married 377/723 (52.1%). Most participants were Catholics 354/723 (49.0%), Acholi 446/723 (61.7%), and from Gulu district 364/723 (50.4%).

Most had secondary level of education 237/723 (32.8%), non-health workers 518/723 (71.7%), and Ugandans by nationality 720/723(99.6%), Africans by race 721/723(99.7%), did not smoke cigarettes 699/723 (96.7%), never drank alcohol 521/723 (72.1%), had no comorbidities 520/723 (71.9%), most agreed that vaccines in health facilities in northern Uganda were safe 250/723 (34.6%), and most had no health insurance coverage 666/723 (92.1%) (Table 1).

Participants' ages were normally distributed with a mean age of 31.4 years SD±10.1 at (95%CI: 30.62-32.10), median age of 30 years, minimum age of 18 years, and maximum of 75 years. The interquartile range was 14 years with a range of 57 (Figure 1).

Participants' perceptions and views on COVID-19 in northern Uganda were that most of them had been exposed to coronavirus 407/723 (56.29%); most were worried about getting infected with the virus 491/723 (67.91%); most had got vaccinated with COVID-19 vaccines 580/723 (80.22%); most had been vaccinated with AstraZeneca 414/723 (57.26%) and had received all two doses of the vaccine 392/723 (54.22%) (Table 2).

The reasons why participants accepted COVID-19 vaccines (taking a COVID-19 vaccine jab) at bivariable analysis were; participants considered prior exposure to the COVID-19, χ^2=5.183; p=0.023; the fear of getting infected with the virus, χ^2=14.614;p<0.000; the fear of death, χ^2=4.892; p=0.027; the fear of a family member getting infected, χ^2=3.679; p=0.055; worries of being forced to take COVID-19 medications, χ^2=4.661; p=0.031; worries of being forced to take COVID-19 vaccines, χ^2=8.297; p=0.004; and those who had no worries about COVID-19 vaccines, χ^2=13.320; p<0.000 (Table 3).

Symptoms and signs experienced by participants who received COVID-19 vaccines in our study population varied by characteristics. Findings in this study offer significant differences in signs and symptoms shared among age-groups, especially excessive sweating, χ^2=10.163;p=0.038 and the fear of death, χ^2=16.608; p=0.002 among older age-groups.

Joint pains, χ^2=13.633; p=0.058; loss of appetite, χ^2=16.573; p=0.020; blood clots χ^2=22.710; p=0.002; the fear of death χ^2=35.083; p<0.000, and excessive sweating χ^2=24.31; p=0.001 were reported among participants from districts.

Blood clots χ^2=18.431; p=0.002 and fear of death χ^2=14.298; p=0.014 were reported at different educational levels of participants. For occupation, blood clots χ^2=8.656; p=0.003 and the fear of death χ^2=4.936; p=0.026 were reported, while blood clots χ^2=7.878; p=0.005 and the fear of death χ^2=15.454; p=0.000 were reported among participants with comorbidities (Table 4).

Table 5 shows the preferred COVID-19 vaccine taken by participants (N=723). The table shows there was a substantial difference between males and females in the COVID-19 vaccine taken χ^2=22.362; p=0.001; age-groups χ^2=52.887; p=0.001; religious groups χ^2=36.560; p=0.048; districts χ^2=83.192; p<0.000; tribes χ^2=43.666; p=0.008; and among those with and without comorbidities χ^2=23.532; p=0.001.

Furthermore, multivariable logistic regression analyses were conducted to determine factors associated with COVID-19 vaccine acceptance among this study population. The analysis found that participants who disagree that vaccines in health facilities in northern Uganda were safe, were 1.98 times more likely to accept COVID-19 vaccines, (aOR=1.98,95% CI: 1.01-3.89; p=0.046) and participants who strongly disagree that vaccines in health facilities in northern Uganda were safe, were 3.31 times more likely to accept COVID-19 vaccines (OR=3.31, 95% CI:1.49-7.36; p=0.003) than those who strongly agree, respectively. Participants from Gulu district were 5.19 times more likely to accept COVID-19 vaccines (aOR=5.19,95% CI:1.71-15.80; p=0.004); Kitgum district were 6.05 times more likely (a OR=6.05, 95% CI:1.76-20.80; p=0.004); and Pader district were 3.45 times more likely to accept COVID-19 vaccines (aOR=3.45,95% CI:1.07-11.14; p=0.038) than Lamwo district, respectively; smokers were 7.75 times more likely to accept COVID-19 vaccines (aOR=7.75,95% CI: 2.06-29.23; p=0.002) than non-smokers; females were 1.95 times more likely to accept COVID-19 vaccines (aOR=1.95,95% CI:1.04-2.42; p=0.032) than males; Baganda tribe were 5.19 times more likely to accept COVID-19 vaccines (a OR= 5.19,95% CI:1.71-15.80; p=0.004); and other tribes (Alur, Basoga, Banyoro) were 6.05 times more likely to accept COVID-19 vaccines (OR= 6.05,95% CI:1.76-20.80; p=0.004) than Itesot tribe, respectively; non-health-workers were 1.74 times more likely to accept COVID-19 vaccines (aOR=1.74,95% CI:1.03-2.96; p=0.040) than health workers. However, participants with comorbidities (aOR = 0.42,95% CI:0.24-0.71; p=0.001) were 58% less likely to accept COVID-19 vaccines than those who did not have; graduates were 58% less likely to accept COVID-19 vaccines (aOR=0.42,95% CI:0.18-0.99; p=0.049) than participants with primary education; and age-group of 20-29 years were 48% less likely to accept COVID-19 vaccines (OR= 0.52,95% CI:0. 31-0.86; p=0.011) than 30-39 year age-group (Table 6).

A map showing Acholi subregion and the nine districts is presented showing the health facilities where this study was conducted. A near-uniform distribution of health facilities in the region has been noted, indicating that findings from our study are representative of the region's population (Figure 2).

Table 1: The Socio-Demographic Characteristics of Participants in Northern Uganda

Variables	Frequency (N=723)	Percent (%)
Sex		
Female	329	45.5
Male	394	54.5
Age (years)		
Less than 20	80	11.1
20-29	279	38.6
30-39	225	31.1
40-49	95	13.1
50 and above	44	6.1
Marital status		
Never married	316	43.7
Married	377	52.1

Others	30	4.1
Religions		
Catholic	354	49.0
Protestant	226	31.3
Others	143	19.8
Tribes		
Acholi	446	61.7
Itesot	22	3.0
Lango	82	11.3
Baganda	49	6.8
Others	124	17.2
Districts		
Agago	83	11.5
Amuru, Nwoya and Omoro	25	3.5
Gulu	364	50.3
Kitgum	57	7.9
Lamwo	62	8.6
Pader	132	18.3
Level of education		
No education	18	2.5
Primary	61	8.4
Secondary	237	32.8
Diploma	146	20.2
Graduate	200	27.7
Postgraduate	61	8.4
Occupations		
Health worker	205	28.4
Non-health worker	518	71.6
Nationality		
Ugandan	720	99.6
Others	3	0.4
Race		
African	721	99.7
European	2	0.3
Health insurance coverage		
No	666	92.1
Yes	57	7.9
Smoking status		
No	699	96.7
Smoker	12	1.7
Ex-Smoker	12	1.7
Alcohol use status		
Never drank	521	72.1
Drinks	127	17.6
Quit drinking	75	10.4
Comorbidities		
No	520	71.9
Yes	203	28.1
Vaccines in health facilities in the region are safe		
Strongly Agree	129	17.8
Agree	250	34.6
Neutral	180	24.9
Disagree	113	15.6
Strongly Disagree	51	7.1

Table 1 Shows That Most Participants Were Males 394/723(54.5%); in the Age-Group of 20-29 Years 279/723 (38.6%); Married 377/723 (52.1%); Catholics 354/723 (49.0%); Acholi by Tribe 446/723 (61.7%); From Gulu District 364/723 (50.4%), Had Secondary Level of Education 237/723 (32.8%), Non-Health Workers 518/723 (71.7%); Ugandans by Nationality 720/723 (99.6%); Africans by Race 721/723 (99.7%); Did Not Smoke Cigarettes 699/723 (96.7%); Never Drank Alcohol 521/723 (72.1%); Had No Comorbidities 520/723 (71.9%); Agreed That Vaccines in Health Facilities in the Region Were Safe 250/723 (34.6%); and Had No Health Insurance Coverage 666/723(92.1%).

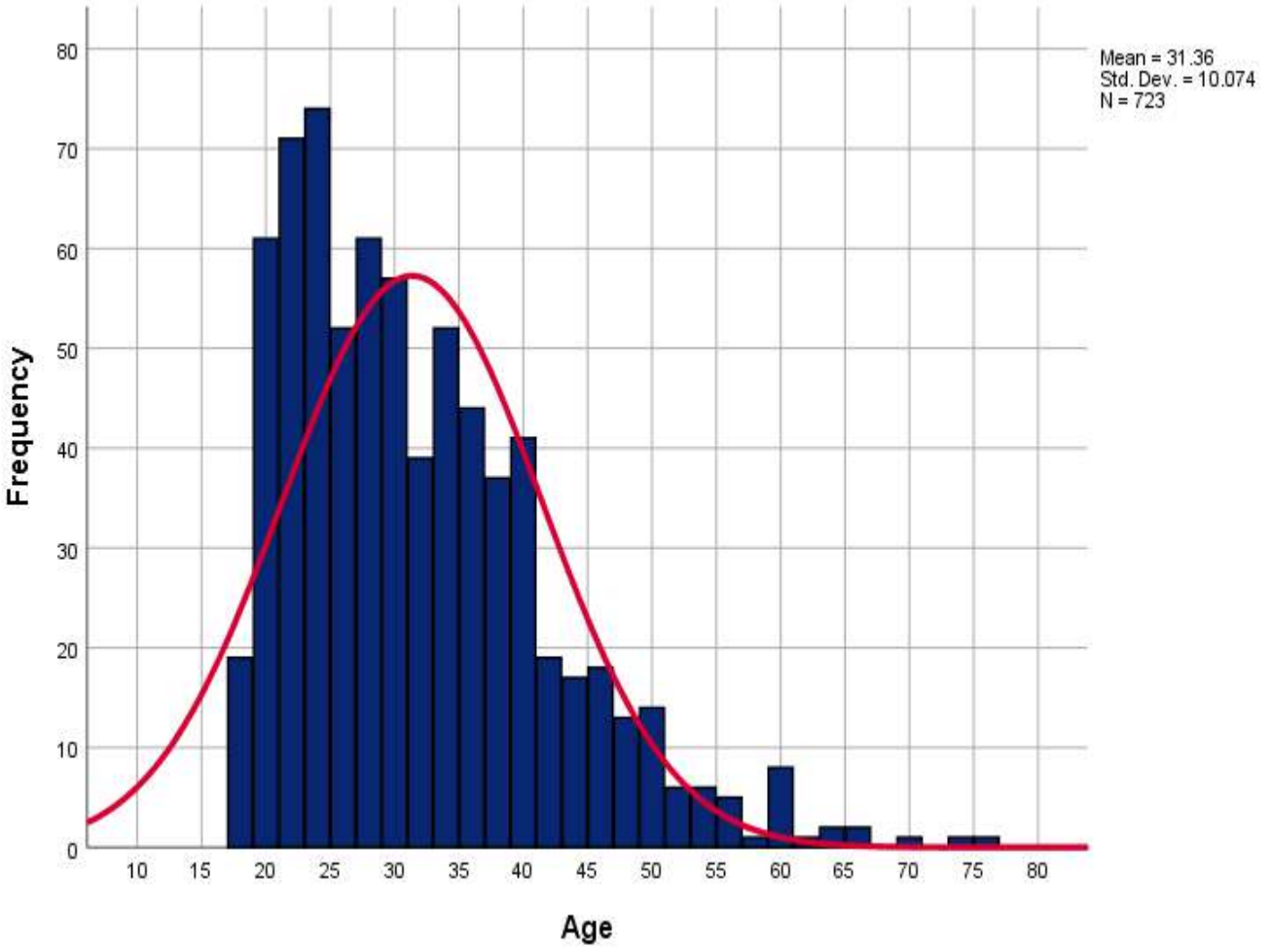

Figure 1: Age Distribution of Participants

Figure 1 is a Histogram Showing an Age Distribution of Participants with a Mean Age of 31.36 Years (SD ±10.07) at 95% CI:30.62-32.10; Median Age of 30 Years, Minimum Age of 18 Years, and a Maximum of 75 Years. the Interquartile Range of 14, and a Range of 57.

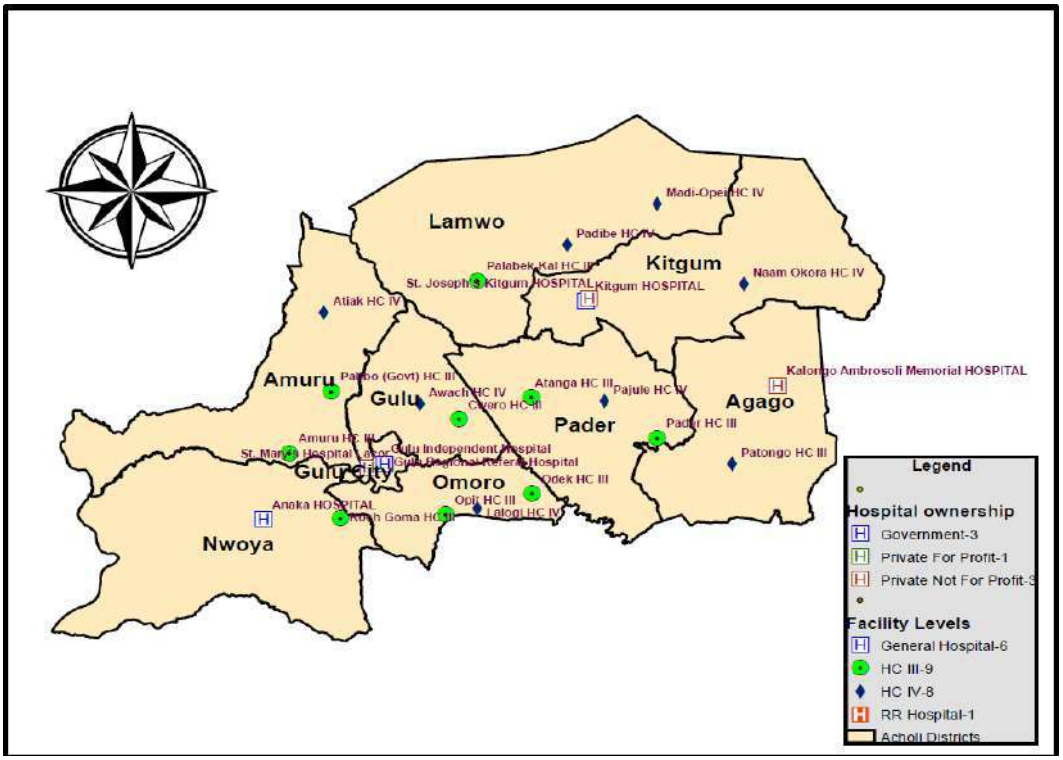

Figure 2: Map Showing Districts and Health Facilities Where the Study Was Conducted in the Acholi Sub-Region of Northern Uganda

Table 2: Participants' Views on COVID-19 and Vaccinations among Participants in Northern Uganda

Variables	Yes (n, %)	No (n, %)
Have you been exposed to coronavirus?	407(56.3)	316(43.7)
What are you most worried about during this COVID-19 pandemic?		
The fear of getting infected with coronavirus	491(67.9)	232(32.1)
The fear of a family member getting infected with coronavirus	440(60.9)	283(39.1)
The fear of death	462(63.9)	261(36.1)
Financial related worries	325(45.0)	398(55.0)
Food insecurity related worries	163(22.5)	560(77.5)
Unavailability of vaccines	114(15.8)	609(84.2)
Coronavirus is a plot or a conspiracy theory	62(8.6)	661(91.4)
I may be forced to take medicines for coronavirus	59(8.16)	664(91.8)
I may be forced to take COVID-19 vaccines	158(21.9)	565(78.1)
I am not worried about any COVID-19 issues	34(4.7)	689(95.3)
Have you got a jab of the COVID-19 vaccine?	580(80.2)	143(19.8)
Which COVID-19 vaccine have you received?		
AstraZeneca	414(57.3)	
Johnson and Johnson	17(2.4)	
Modena	117(16.2)	
Pfizer	14(2.0)	
Sinovac	13(1.8)	
Sputnik	7(1.0)	
None	141(19.5)	
How many doses of the COVID-19 vaccine have you received?		
One	189(26.1)	
Two	392(54.2)	
None	142(19.6)	

Table 2 Shows That Most Participants Had Been Exposed to Coronavirus 407/723 (56.3%); Were Worried About Getting Infected With Coronavirus 491/723 (67.9%); Had Got Vaccinated With COVID-19 Vaccines 580/723 (80.2%); Had Got Vaccinated With Astra Zeneca 414/723 (57.3%) and Had Received All the Two Doses 392/723 (54.2%).

Table 3: Reasons Why Participants Accepted COVID-19 Vaccines (Taking a Jab) at Bivariable Analysis

	Participants' Responses			
Variables	Yes (n, %)	No (n, %)	χ^2	p-value
Those who were exposed to coronavirus	337(46.6)	243(33.6)	5.183	0.023
The fear of getting infected with coronavirus	413(57.1)	167(23.1)	14.614	0.000
The fear of death	382(52.8)	198(27.1)	4.892	0.027
The fear of a family member getting infected	363(50.2)	217(30.0)	3.679	0.055
Financial worries	268(37.1)	312(43.2)	1.867	0.172
Job-related worries	152(21.0)	428(59.2)	0.183	0.669
Food insecurity worries	134(18.5)	446(61.7)	0.524	0.469
Worries about unavailability of vaccines	96(13.3)	484(66.9)	1.357	0.244
Worries that COVID-19 is a plot or conspiracy theory	47(6.5)	533(73.7)	0.833	0.361
Worries of being forced to take COVID-19 medications	41(5.7)	539(74.6)	4.661	0.031
Worries about being forced to take COVID-19 vaccines	114(15.8)	466(64.5)	8.297	0.004
No worries on issues of COVID-19 vaccines	19(2.6)	561(77.6)	13.32	0.000

Table 3 Shows Reasons Why Participants Accepted COVID-19 Vaccines (Taken a COVID-19 Vaccine Jab) at Bivariable Analysis. Participants Considered Prior Exposure to the Coronavirus $\chi2=5.183$; $p=0.023$; the Fear of Getting Infected $\chi2=14.614$; $p<0.000$; the Fear of Death $\chi2=4.892$; $p=0.027$; the Fear of a Family Member Getting Infected $\chi2=3.679$; $p=0.055$; Worries of Being Forced to Take COVID-19 Medications $\chi2=4.661$;$p=0.031$; Worries of Being Forced to Take a COVID-19 Vaccine $\chi2=8.297$; $p=0.004$; and Those Who Had No Worries About the COVID-19 Vaccines $\chi2=13.320$; $p<0.000$.

Table 4: Symptoms and Signs Experienced by Participants Who Received COVID-19 Vaccines

Variables	Age groups	Marital status	Religion	Tribe	Districts	Level of Education	Occupation	Nationality	Race	Comorbidities
Fever	3.146(p=0.534)	4.786(p=0.310)	2.453(p=0.653)	2.148(p=0.709)	7.582(p=0.371)	4.694(p=0.454)	0.072(p=0.789)	0.224(p=0.974)	0.149(p=0.699)	0.442(p=0.506)
Joint pains	2.069(p=0.723)	1.355(p=0.852)	0.353(p=0.983)	5.094(p=0.278)	13.633(p=0.058)	8.871(p=0.114)	0.264(p=0.607)	0.090(p=0.993)	0.060(p=0.8007)	2.037(p=0.153)
Loss of appetite	3.927(p=0.416)	1.311(p=0.846)	1.592(p=0.810)	6.284(p=0.179)	16.573(p=0.020)	3.593(p=0.609	1.395(p=0.237)	0.025(p=0.999)	0.017(p=0.899)	1.440(p=0.230)
Steven-John son § reaction	4.980(p=0.289)	0.657(p=0.957)	2.455(p=0.653)	7.494(p=0.112)	6.137(p=0.524)	2.722(p=0.743	0.336(p=0.562)	0.021(p=0.999)	0.014(p=0.906)	1.966(p=0.161)
Blot clot	6.509(p=0.164)	4.895(p=0.298)	6.335(p=0.176)	16.284(p=0.003)	22.710(p=0.002)	18.431(p=0.002)	8.656(p=0.003)	6.108(p=0.106)	1.971(p=0.160)	7.878(p=0.005)
Feeling dizzy	0.691(p=0.952)	0.461(p=0.977)	1.549(p=0.818)	8.880(p=0.064)	3.060(p=0.879)	5.532(p=0.354)	0.890(p=0.346)	0.108(p=0.99)	0.072(p=0.789)	1.870(p=0.171)
Death	16.608(p=0.002)	8.350(p=0.080)	6.892(p=0.142)	4.099(p=0.393)	35.083(p=0.000)	14.298(p=0.014)	4.936(p=0.026)	0.307(p=0.946)	0.246(p=0.620)	15.454(p=0.000)
Feeling uncomfortable	4.402(p=0.354)	0.786(p=0.940)	1.762(p=0.779)	3.335(p=0.503)	4.855(p=0.678)	3.971(p=0.554)	1.023(p=0.312)	0.064(p=0.994)	0.042(p=0.837)	1.078(p=0.299)

Body pains and weakness	6.383(p=0.172)	10.042(p=0.040)	5.340(p=0.254)	5.998(p=0.199)	6.898(p=0.440)	8.933(p=0.112)	0.291(p=0.589)	6.842(p=0.077)	0.307(p=0.579)	0.974(p=0.324)
Getting the virus after vaccination	0.880(p=0.927)	18.387(p=0.001)	3.361(p=0.499)	4.538(p=0.503)	11.458(p=0.120)	5.611(p=0.346)	1.001(p=0.317)	0.034(p=0.998)	0.022(p=0.881)	0.038(p=0.846)
Fear of the COVID-19 vaccine	3.636(p=0.458)	0.321(p=0.988)	0.793(p=0.939)	10.482(p=0.033)	2.563(p=0.922)	0.876(p=0.972)	0.037(p=0.848)	0.013(p=0.998)	0.008(p=0.927)	1.176(p=0.278)
Heart complications	7.793(p=0.099)	5.193(p=0.268)	4.412(p=0.353)	2.369(p=0.668)	7.936(p=0.922)	2.683(p =0.749)	0.348(p=0.998)	0.042(p=0.998)	0.028(p=0.867)	2.413(p=0.120)
Excessive sweating	10.163(p=0.038)	0.693(p=0.952)	0.793(p=0.939)	10.158(p=0.038)	24.316(p=0.001)	2.730(p=0.742)	0.037(p=0.848)	0.013(p=1.000)	0.008(p=0.927)	1.176(P=0.278)
No Side-effects	5.088(p=0.278)	0.311(p=0.989)	26.833(p=0.000)	4.812(p=0.307)	7.236(p=0.405)	4.584(p=0.469)	2.394(p=0.122)	0.025(p=0.999)	0.017(p=0.897)	0.390(p=0.532)

Table 4 Shows Significant Differences in Signs and Symptoms Shared Among Age-Groups, Especially Excessive Sweating $\chi2=10.163$; $p=0.038$ and the Fear of Death $\chi2=16.608$; $p=0.002$, Among Older Age-Groups. Joint Pains $\chi2=13.633$; $p=0.058$, Loss of Appetite $\chi2=16.573$; $p=0.020$, Blood Clots $\chi2=22.710$; $p=0.002$, the Fear of Death $\chi2=35.083$; $p=0.000$, and Excessive Sweating $\chi2=24.316$; $p=0.001$ Were Common in Districts. Blood Clots $\chi2=18.431$;$p=0.002$ and the Fear of Death $\chi2=14.298$; $p=0.014$ Were Reported at Levels of Education. for Occupation, Blood Clots $\chi2=8.656$; $p=0.003$ and the Fear of Death $\chi2=4.936$; $p=0.02$ and Finally, Blood Clots $\chi2=7.878$; $p=0.005$and the Fear of Death $\chi2=15.454$; $p<0.000$ Were Reported Among Participants With Comorbidities.

Table 5: The Preferred COVID-19 Vaccine Among Participants (N=723) at Bivariable Analysis Using Chi Square Test

	Variables	AZ	J&J	Moderna	Pfizer	Sinovac	Sputnik	None	Chi	df	p-value
1	**Sex**										
	Female	91(12.6%)	109(15.1%)	34(4.7%)	6(0.8%)	0(0.0%)	1(0.1%)	88(12.2%)	22.362	6	0.001
	Male	115(15.9%)	141(19.5%)	26(3.6%)	30(4.1%)	3(0.4%)	2(0.3%)	77(10.7%)			
2	**Age groups (years)**										
	<20	21(2.9%)	28(3.9%)	8(1.1%)	4(0.6%)	0(0.0%)	0(0.0%)	19(2.6%)	52.877	24	0.001
	20-29	77(10.7%)	82(11.3%)	25(3.5%)	14(1.9%)	1(0.1%)	1(0.1%)	78(10.84%)			
	30-39	73(10.19%)	79(10.9%)	12(1.7%)	15(2.1%)	0(0.0%)	0(0.0%)	45(6.2%)			
	40-49	21(2.9%)	42(5.8%)	15(2.1%)	2(0.3%)	0(0.0%)	0(0.0%)	15(2.1%)			
	≥50	14(1.9%)	19(2.6%)	0(0.0%)	1(0.1%)	2(0.3%)	2(0.3%)	8(1.1%)			
3	**Marital status**										
	Divorced	4(0.6%)	11(1.5%)	1(0.1%)	0(0.0%)	0(0.0%)	0(0.0%)	7(1.0%)	20.763	24	0.653
	Married	99(13.7%)	141(19.5%)	37(5.1%)	16(2.2%)	2(0.3%)	3(0.4%)	79(10.9%)			
	Separated	1(0.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)			
	Single	100(13.8%)	96(13.3%)	21(2.9%)	20(2.8%)	1(0.1%)	0(0.0%)	1(0.1%)			
	widowed	2(0.3%)	2(0.3%)	1(0.1%)	0(0.0%)	0(0.0%)	0(0.0%)	78(10.8%)			
4	**Religion**										
	Born Again	28(3.9%)	31(4.3%)	7(1.0%)	9(1.2%)	0(0.0%)	1(0.1%)	36(5.0%)	36.56	24	0.048
	Catholics	98(13.6%)	142(19.6%)	21(2.9%)	16(2.2%)	2(0.3%)	2(0.3%)	73(10.1%)			
	Muslims	7(1.0%)	8(1.1%)	4(0.6%)	1(0.1%)	0(0.0%)	0(0.0%)	6(0.8%)			
	Protestants	69(9.5%)	69(9.5%)	28(3.9%)	9(1.2%)	1(0.1%)	0(0.0%)	50(6.9%)			
	Others	4(0.6%)	0(0.0%)	0(0.0%)	1(0.1%)	0(0.0%)	0(0.0%)	0(0.0%)			
5	**Tribes**										
	Acholi	130(18.0%)	163(22.3%)	38(5.3%)	10(1.4%)	3(0.4%)	3(0.4%)	99(13.7%)	43.666	24	0.008
	Itesot	7(1.0%)	9(1.2%)	1(0.1%)	2(0.4%)	0(0.0%)	0(0.0%)	3(0.4%)			
	Lango	25(3.5%)	24(3.3%)	9(1.2%)	2(0.3%)	0(0.0%)	0(0.0%)	0(0.0%)			
	Baganda	15(2.1%)	16(2.2%)	2(0.3%)	8(1.1%)	0(0.0%)	0(0.0%)	0(0.0%)			
	Others	29(4.0%)	38(5.3%)	10(1.4%)	14(1.9%)	0(0.0%)	0(0.0%)	33(4.6%)			
6	**Districts**										
	Agago	28(3.8%)	22(3.0%)	8(1.1%)	0(0.0%)	1(0.1%)	0(0.0%)	24(3.3%)	83.912	42	0.000
	Amuru	4(0.6%)	1(0.1%)	1(0.1%)	1(0.1%)	0(0.0%)	0(0.0%)	5(0.7%)			
	Gulu	105(14.5%)	111(15.4%)	19(2.6%)	28(3.9%)	2(0.3%)	0(0.0%)	99(13.7%)			
	Kitgum	20(2.8%)	19(2.6%)	8(1.1%)	2(0.3%)	0(0.0%)	0(0.0%)	8(1.1%)			
	Lamwo	17(2.4%)	26(3.6%)	10(1.4%)	2(0.3%)	0(0.0%)	1(0.1%)	6(0.8%)			
	Nwoya	1(0.1%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	3(0.4%)			
	Omoro	4(0.6%)	5(0.7%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)			
	Pader	27(3.7%)	66(9.1%)	14(1.9%)	3(0.4%)	0(0.0%)	2(0.3%)	20(2.8%)			

7	**Level of education**									
	No education	3(04%)	7(1.0%)	2(0.3%)	0(0.0%)	0(0.0%)	1(0.1%)	5(0.7%)	39.053	30	0.125
	Primary	15(2.1%)	22(3.0%)	7(1.0%)	3(0.4%)	0(0.0%)	0(0.0%)	14(1.9%)			
	Secondary	74(10.2%)	77(10.7%)	24(3.3%)	10(1.4%)	0(0.0%)	2(0.3%)	50(6.9%)			
	Diploma	37(5.1%)	58(8.0%)	12(1.7%)	10(1.4%)	2(0.3%)	0(0.0%)	27(3.7%)			
	Degree	61(8.4%)	70(9.7%)	11(1.5%)	11(1.5%)	1(0.1%)	0(0.0%)	46(6.4%)			
	Postgraduate	16(2.2%)	16(2.2%)	4(0.6%)	2(0.3%)	0(0.0%)	0(0.0%)	23(3.2%)			
8	**Occupations**									
	Health workers	60(8.3%)	78(10.8%)	13(1.8%)	12(1.7%)	0(0.0%)	0(0.0%)	42(5.8%)			
	Non-health workers	146(20.2%)	172(23.8%)	47(6.5%)	123(19.0%)	24(3.3%)	3(0.4%)	3(0.4%)	5.875	6	0.437
9	**Health Insurance coverage**									
	Yes	20(2.8%)	18(2.5%)	3(0.4%)	2(0.3%)	0(0.0%)	0(0.0%)	14(1.4%)	2.657	6	0.850
	No	186(25.7%)	232(32.1%)	57(7.9%)	34(4.7%)	3(0.4%)	3(0.4%)	151(20.9%)			
10	**Comorbidities**									
	Yes	46(6.4%)	78(10.8%)	27(3.7%)	11(1.5%)	1(0.1%)	3(0.4%)	37(5.1%)	23.532	6	0.001
	No	160(22.1%)	172(23.8%)	33(4.6%)	25(3.5%)	2(0.3%)	0(0.0%)	128(17.7%)			

Table 5 Shows That There Was a Significant Difference in the Preferred COVID-19 Vaccine Jab Taken Between Males and Females $\chi2=22.362$; p=0.001; Age-Groups $\chi2=52.887$; p=0.001; Religious Groups $\chi2=36.560$; p=0.048; Districts $\chi2=83.192$; p=0.000; Tribal Groups $\chi2=43.666$;p=0.008; Those With and Without Comorbidities $\chi2=23.532$;p=0.001

Table 6: Bi-Variable and Multivariable Analysis of COVID-19 Vaccine Acceptance (N=723) Among Participants

Variables	Vaccinated (N=580) (n, %)	Not Vaccinated (N=143) (n, %)	Unadjusted COR	95% CI	p value	Adjusted OR	95% CI	p value
Sex								
Male	324 (82.2)	70 (17.8)	**Reference**			**Reference**		
Female	256 (77.8)	73 (22.2)	1.320	(0.915- 1.904)	0.138	1.587	(1.042-2.418)	0.032
Age (years)								
30-39	174 (77.3)	51 (22.7)	**Reference**			**Reference**		
Less than 20	62 (77.5)	18 (22.5)	0.991	(0.538-1.824)	0.976	0.490	(0.236-1.018)	0.056
20-29	228 (81.7)	51 (18.3)	0.763	(0.494-1.180)	0.224	0.517	(0.311-0.859)	0.011
40-49	77 (81.1)	18 (18.9)	0.798	(0.437-1.454)	0.460	0.796	(0.405-1.566)	0.509
50 and above	39 (88.6)	5 (11.4)	0.437	(0.164-1.168)	0.099	0.478	(0.158-1.447)	0.191
Marital status								
Others	24 (80.0)	6 (20.0)	**Reference**					
Never married	255 (80.7)	61 (19.3)	0.957	(0.375-2.443)	0.927			
Married	301 (79.8)	76 (20.2)	1.010	(0.399-2.558)	0.983			
Religion								
Protestant	176 (77.9)	50 (22.1)	**Reference**			**Reference**		
Catholic	295 (83.3)	59 (16.7)	0.704	(0.704-1.072)	0.102	0.653	(0.409-1.044)	0.075
Others	109 (76.2)	34 (23.8)	1.098	(1.098-1.805)	0.712	1.013	(0.581-1.768)	0.963
Tribe								
Itesot	19 (86.4)	3 (13.6)	**Reference**			**Reference**		
Acholi	353 (79.1)	93 (20.9)	1.669	(0.483-5.760)	0.418	1.292	(0.337-4.959)	0.709
Lango	69 (84.1)	13 (15.9)	1.193	(0.308-4.622)	0.798	2.921	(0.613-13.922)	0.179
Muganda	44 (89.8)	5 (10.2)	0.720	(0.156-3.321)	0.673	5.193	(1.707-15.804)	0.004
Others	95 (76.6)	29 (23.4)	1.933	(0.534-7.000)	0.315	6.046	(1.758-20.801)	0.004
Districts								
Lamwo	58 (93.5)	4 (6.5)	**Reference**			**Reference**		
Agago	76 (91.6)	7 (8.4)	1.336	(0.373-4.780)	0.657	1.292	(0.337-4.959)	0.709
Amuru Nwoya and Omoro	21 (84.0)	4 (16.0)	2.762	(0.633-12.049)	0.176	2.921	(0.613-13.922)	0.179
Gulu	276 (75.8)	88 (24.2)	4.623	(1.632-13.096)	0.004	5.193	(1.707-15.804)	0.004
Kitgum	41 (71.9)	16 (28.1)	5.659	(1.763-18.165)	0.004	6.046	(1.758-20.801)	0.004
Pader	108 (81.8)	24 (18.2)	3.222	(1.067-9.734)	0.038	3.450	(1.068-11.144)	0.038

Level of education								
Primary	49 (80.3)	12 (19.7)	**Reference**			**Reference**		
No formal education	14 (77.8)	4 (22.2)	1.167	(0.325-4.188)	0.813	0.697	(0.163-2.976)	0.626
Secondary	183 (77.2)	54 (22.8)	1.205	(0.598-2.428)	0.602	0.950	(0.438-2.057)	0.896
Diploma	118 (80.8)	28 (19.2)	0.969	(0.456-2.059)	0.935	0.669	(0.277-1.614)	0.371
Graduate	175 (87.5)	25 (12.5)	0.583	(0.273-1.244)	0.163	0.419	(0.177-0.995)	0.049
Postgraduate	41 (67.2)	20 (32.8)	1.992	(0.871-4.555)	0.103	1.278	(0.486-3.360)	0.619
Occupations								
Health workers	175 (85.4)	30 (14.6)	**Reference**			**Reference**		
Non-health Workers	405 (78.2)	113 (21.8)	1.628	(1.048- 2.527)	0.030	1.742	(1.025-2.958)	0.04
Nationality								
Ugandan	577 (80.1)	143 (19.9)	**Reference**					
Others	3 (100)	0 (0.0)	0	0	0.999			
Race								
African	578 (80.2)	143 (19.8)	**Reference**					
European	2 (100)	0 (0.0)	0	0	0.999			
Health Insurance coverage								
No	538 (80.8)	128 (19.2)	**Reference**			**Reference**		
Yes	42 (73.7)	15 (26.3)	1.501	(0.807-0.791)	0.199	1.278	(0.636-2.568)	0.49
Smoking Status								
No	564 (80.7)	135 (19.3)	**Reference**			**Reference**		
Smoker	6 (50.0)	6 (50.0)	4.178	(1.327-13.156)	0.015	7.754	(2.057-29.232)	0.002
Ex-smoker	10 (83.3)	2 (16.7)	0.836	(0.181-3.858)	0.818	1.215	(0.210-7.020)	0.828
Alcohol drinking status								
Never drank	425 (81.6)	96 (18.4)	**Reference**					
Drinks	98 (77.2)	29 (22.8)	1.310	(0.819-2.096)	0.260			
Quit drinking	57 (76.0)	18 (24.0)	1.398	(0.787-2.483)	0.253			
Comorbidities								
No	405 (77.9)	115 (22.1)	**Reference**			**Reference**		
Yes	175 (86.2)	28 (13.8)	0.563	(0.359-0.883)	0.012	0.419	(0.248-0.708)	
Vaccines in our health facilities are safe								0.001
Strongly Agree	108 (83.7)	21 (16.3)	**Reference**			**Reference**		
Agree	216 (86.4)	34 (13.6)	0.810	(0.448-1.462)	0.483	0.824	(0.436-1.558)	0.552
Neutral	146 (81.8)	34 (18.9)	1.198	(.658-2.178)	0.555	1.060	(0.552-2.038)	0.86
Disagree	77 (68.1)	36 (31.9)	2.404	(1.303-4.436)	0.005	1.984	(1.011-3.894)	0.046
Strongly Disagree	33 (64.7)	18 (35.3)	2.805	(1.338-5.882)	0.006	3.308	(1.487-7.360)	0.003

Table 6 shows factors associated with COVID-19 vaccine acceptance among participants in northern Uganda. Participants who disagree that vaccines in health facilities in northern Uganda were safe, aOR=1.98,95% CI:1.01-3.89; p=0.046 and participants who strongly disagree that vaccines in health facilities in northern Uganda were safe aOR=3.31,95% CI:1.49-7.36; p=0.003 compared to those who strongly agree; participants from Gulu district aOR=5.19,95% CI:1.71-15.80; p=0.004; Kitgum district aOR=6.05,95% CI:1.76-20.80; p=0.004; Pader district aOR=3.45,95% CI:1.07-11.14; p=0.038 compared to Lamwo district, smokers aOR=7.75,95% CI:2.06-29.23; p=0.002 compared to non-smokers; females aOR=1.95,95% CI:1.04-2.42; p=0.032 compared to males; Baganda tribe aOR=5.19,95% CI:1.71-15.80; p=0.004; and Other tribes (Alur, Basoga, Banyoro) aOR=6.05,95% CI:1.76-20.80; p=0.004 compared to Itesot; and non-health-workers aOR=1.74,95% CI:1.03-2.96; p=0.040 compared to health workers. However, participants with comorbidities aOR=0.42,95% CI:0.24-0.71;p=0.001 were less likely to accept COVID-19 vaccines than those who did not have; Graduates were less likely to accept COVID-19 vaccines aOR=0.42,95% CI:0.18-0.99; p=0.049 than participants with primary education; and age-group of 20-29 years aOR=0.52,95% CI:0.31-0.86; p=0.011 than 30-39 year age-group.

IV. DISCUSSION

The most significant finding from this study population (Table 1, Figure 1, Figure 2) was that COVID-19 vaccine acceptance in northern Uganda was high at 580/723 (80.2%, 95% CI:78.9%-83.4%). This finding contrasts with a study by Kabagenyi *et al,* in Uganda (2022) which observed a low COVID-19 vaccine acceptance at 41.4% [24]. However, that study noted substantial regional variations in vaccine hesitancy where a lower COVID-19 vaccine hesitancy was observed in participants from northern and eastern Uganda compared to western and central Uganda [24], a finding which is like our study findings (Table 2, Table 3, Table 4, Table 5). The authors argued that the lower vaccine hesitancy in northern Ugandan population compared to central and western Uganda was due to prior Ugandan Ministry of Health mobilization and roll out of information on COVID-19 vaccines, dispelling misconceptions, myths, and conspiracy theories about COVID-19 vaccines and thus the higher vaccine acceptance rate [24].

Thus, the high COVID-19 vaccine acceptance rate is likely because of the commendable work of health managers in northern Uganda for conducting consistent community sensitization, mobilization, and engagements using village health teams (VHTs), which helped turn a vaccine-hesitant/inquisitive population to the opposite. This finding is consistent with others that stakeholder engagement, social mobilization, and equitable distribution of vaccines increase vaccine acceptance in low-to-middle-income countries [25,26,27]. Accordingly, we, the authors propose that the approach used to achieve this high COVID-19 vaccine acceptance rate in northern Uganda could be replicated in other parts of Uganda, especially using VHTs as agents of change.

The current study's finding that female gender was significantly associated with COVID-19 vaccine acceptance is not new (females 77.8% versus males 82.2%) (Table 6) but contrasts another observed in Kabagenyi, *et al.,* (aOR=0.77,95% CI:0.58-1.02) in Uganda [24] but consistent with other studies elsewhere [28,29]. For example, high COVID-19 vaccine acceptance rates were recorded among pregnant women in northwestern Ethiopia [28] and Saudi Arabia [29].

Relatedly, many studies in Uganda show that females have better health-seeking behaviors than males [30,31,32,33]. Females' better health-seeking behaviors than males have been similarly observed during implementation of many health activities among communities in northern Uganda [31]. In addition, experience from Uganda shows that females are more receptive to health messages from Ugandan government and have always been at the forefront of fighting against many infectious diseases, including malaria [32]. Thus, their compliance with health messages from the Ugandan Ministry of Health has always been positive. This experience includes reproductive health services, vaccination of children, voluntary counseling, and testing (VCT) for HIV and AIDs, cancer screening, and many health prevention and promotion activities [33].

However, a systematic review and meta-analysis by Stephanie showed that males had more likely intentions of getting vaccinated against COVID-19 than females [34]. In contrast, our current study showed that it was more likely for females to accept COVID-19 vaccines than males (Table 6). This finding is likely because of disinformation, misinformation, and numerous conspiracy theories circulating in the community through social and other media sources about COVID-19 vaccines that may have affected males more than females but also highlights deeper problems on health seeking behaviors among males in northern Uganda. For similar reasons, non-health workers were more likely to accept COVID-19 vaccines compared to health workers and this is consistent with the findings from Amuru district in Uganda [7], sub-Saharan Africa [13] and Kuwait and Jordan [14]. Furthermore, the Baganda tribe who were resident in northern Uganda were more likely to accept COVID-19 vaccines (89.8% versus 10.2%) (Table 6) due to the fear of death, experience of suffering from the illness and caring for loved ones during the second wave of COVID-19 that was more severe in central Uganda where the majority tribe are

Baganda compared to the north (Table 2 and Table 3). It is also important to note that participants in our study raised many issues regarding the reasons for accepting COVID-19 vaccines ranging from the fear of death, the fear of contracting the virus and infecting family members. We, the authors argue that the fear factor and experience of COVID-19 during the second wave may have in many ways contributed to the vaccine acceptance among this sector of the study population (Table 2 and Table 3).

Also, our study found that participants with comorbidities were less likely to accept COVID-19 vaccines than those without (86.2% versus 77.9%, aOR=0.50, 95% CI:0.30-0.82; p=0.006); age-group of 20-29 years were less likely to accept COVID-19 vaccines (81.7% versus 18.3%, aOR=0.52, 95% CI:0.31-0.86; p=0.011) than 30-39 year age-group, and graduates were less likely to accept the vaccine (87.5% versus 12.5%, aOR=0.42,95% CI:0.18-0.99; p=0.049) than participants with primary level of education (Table 6). This finding among persons with comorbidities is inconsistent with many studies in Uganda, which showed participants with comorbidities, particularly diabetes, hyper tension, obesity, heart diseases, chronic obstructive pulmonary diseases (COPD), HIV, and AIDS, were more at risk of developing severe COVID-19 illness, and higher chances of hospitalization, and death [35-40].

Note that despite persistent messages on the increased risks and susceptibility to coronavirus, with higher chances of acquiring the more severe form of the disease, higher chances of hospitalization, and death among the most at-risk population which the mainstream and social media had widely covered and that most people had become aware, the COVID-19 vaccine acceptance was less likely in participants with comorbidity in our study population (Table 6). In addition, the Ugandan Ministry of Health had prioritized vaccination of the elderly and those with comorbidities in the early phases of COVID-19 vaccine roll-out in Uganda [36].

Of special interest was a finding in Kabagambe, *et al.,* that a significant proportion of Ugandan population had misconceptions that COVID-19 vaccines could spread coronavirus in the body, that the virus kills people with underlying conditions, and that the COVID-19 vaccine could make them infertile [24]. In addition, others doubted the existence of the virus and the safety of the vaccine itself [24]. This information could have likely been responsible in part for the COVID-19 vaccine hesitancy among the comorbid population, age-group of 20-29 years, and graduates in our study (Table 6).

Meanwhile, in other participants in this study population, COVID-19 vaccine acceptance was high for many reasons, including the fear of getting infected, the fear of infecting family members, the fear of death, and worries that COVID-19 medications would be forced on them if they did not get vaccinated (Table 3 and Table 4).

Most notable was, however that the COVID-19 vaccine preferred by each participant in our study population was provided by the Government of Uganda through the Ministry of Health, and choices on the type of COVID-19 vaccine were participant's decision (Table 5).

Furthermore, some participants and their associates had tested positive for coronavirus and had experienced the disease, which perhaps impacted their decision to get vaccinated (Table 2, Table 3, and Table 4). So, we, the authors argue that whereas COVID-19 vaccination was a timely intervention by the Ugandan Ministry of Health, participants with comorbidities were less likely to accept COVID-19 vaccines (Table 6). Could they have been adversely affected by misinformation and disinformation on COVID-19 vaccines that hard-pressed them to refuse COVID-19 vaccines? The authors suggest that, in the future, a comprehensive study particularly a qualitative study should be conducted to assess in detail the reasons why participants with comorbidities, graduates, and age-group of 20-29 years hesitated to take COVID-19 vaccines.

Likewise, COVID-19 vaccine acceptance was more likely among participants from Gulu, Kitgum, and Pader districts, smokers, non-health workers, females, those who disagree and strongly disagree

that vaccines in health facilities in northern Uganda were safe compared to participants who strongly agree (Table 6).

Participants from districts of Gulu 276/364 (75.8%), Kitgum 41/57 (71.9%), and Pader 108/132 (81.8%) were more likely to accept COVID-19 vaccines compared to Lamwo district (Table 6). On this finding, studies show that vaccine acceptance is linked to community's confidence in healthcare systems, health workers, cultural backgrounds, attitudes, beliefs, perceptions, political, environmental, personal factors, and compliance with face mask-wearing guidelines [11,41,42,43].

We, the authors, found that the three districts, just like others in Uganda, set up COVID-19 district task forces layered to the village health teams (VHTs) who promoted COVID-19 vaccinations at local levels [43]. The village health teams are vital in connecting communities to the Ugandan healthcare system [43]. We, the Authors, argue that VHTs' roles in disease prevention, promotion and control in Ugandan healthcare system need to be rated more by policymakers.

Nevertheless, VHTs are critical change agents, and their position in Ugandan health delivery system should be promoted to enhance their contributions to the healthcare system [44]. This finding implies that for the Ugandan Ministry of Health to achieve higher COVID-19 vaccine acceptance rates, layered task forces up to the village level and using VHTs for campaigns could be adopted [44]. The authors argue that VHTs played a considerable role in convincing the community to accept COVID-19 vaccines in the three districts [44].

Further, the finding that smokers in this study population were more likely to accept COVID-19 vaccines than non-smokers and ex-smokers have attracted much interest (Table 6). These participants could have been more confident in COVID-19 vaccines' ability to reduce the virus's chances of infecting them. More so, this virus being a respiratory disease could have swayed them by the fear factor and worries about getting infected or being forced to take medications if they missed out on their COVID-19 jabs (Table 3).

This finding is like one in a refugee camp in Bidibidi in Uganda where the authors found that COVID-19 vaccine acceptance rate among refugees was 78% and was associated with beliefs that COVID-19 vaccines could stop the spread of coronavirus [45] as similarly seen in these groups of smokers (Table 6). In addition, findings show that respondents who were uncertain whether COVID-19 vaccines would stop transmissions were less likely to get the vaccine (aOR=0.70; 95%CI=0.51-0.96) than confident respondents. In that study, respondents who did not want to go to health facilities (aOR=0.61;95%CI=0.44-0.84) were also less likely to accept COVID-19 vaccines than counterparts who wanted to go to health facilities [45].

Lastly, our finding that participants that strongly disagree and disagree on the safety of vaccines in health facilities in northern Uganda were three and two times more likely to accept COVID-19 vaccines compared to participants who strongly agree, respectively, raised our interests (Table 6). This finding is unique as most previous studies show that the confidence and trust in healthcare systems were among the most likely reasons for vaccine acceptance [6,14,15,41-43]. We, the authors, intend to explore these responses from our participants in a future qualitative study. Could it have been that this finding was an isolated response or specifically seen with COVID-19 vaccines in northern Uganda? We, the authors argue that it may be too early to determine what exactly it is until a comprehensive analysis has been completed in future studies.

In summary, our current study found a high COVID-19 vaccine acceptance rate of 580/723(80.2%) in an adult population in northern Uganda. This survey was conducted after the second wave of COVID-19 in Uganda when many high-profile persons had lost their lives compared to the first wave. In addition, this current acceptance rate in northern Uganda was lower than a South African study at 90% [15] but higher than a Somali study at 77% [16] and another Ugandan study at 60% [8]. Whether the

high burden of COVID-19 in South Africa could have contributed to the substantially higher vaccine acceptance rate will be reviewed in future studies.

Therefore, we, the authors propose that the most effective strategy for reducing COVID-19 vaccine hesitancy in the Ugandan setting should include educating the population on COVID-19 and vaccines. The authors propose that educating people through a community engagement strategy is the most optimum way of dispelling myths, misconceptions, rumors, conspiracy theories, and fears about coronavirus. Thus, we propose that encouraging healthy behaviors towards coronavirus will keep Ugandans safe, a virus that has ravaged the world so much.

Finally, findings from other Ugandan studies indicate a high COVID-19 vaccine hesitancy in the general population. However, our findings are inconsistent with theirs and have a higher COVID-19 vaccine acceptance rate. Therefore, we, the authors, question and continue to ask more questions whether the suspected high COVID-19 vaccine hesitancy among the Ugandan population could have been a vaccine inquisitiveness rather than vaccine hesitancy. The higher COVID-19 vaccine acceptance among this study population in northern Uganda compared to others favors the understanding that the situation was more of COVID-19 vaccine inquisitiveness rather than COVID-19 vaccine hesitancy.

4.1 Strengths and Limitations of this Study

Our study has many strengths. First, this data is vital as it is one of the few well-documented and completed data on 723 participants from the Acholi sub-region regarding COVID-19 vaccine acceptance in the recent period. Second, findings from this study show a higher COVID-19 vaccine acceptance rate despite differing results from other parts of Uganda. Third, we used a systematic sampling method, a probability sampling method which is vital for the study's results. Finally, using a validated questionnaire helped us obtain this information which is generalizable in the context.

However, this study had limitations in the design, a cross-sectional study where one-time information from participants is gathered and analyzed. These have shortcomings in that, views and opinions of participants are dynamic; they vary according to prevailing environmental situations. In this, we suggest a need for future prospective or a longitudinal assessment of COVID-19 vaccine acceptance in future, ensuring that all data are measured and recorded accordingly.

4.2 Generalizability of Results

These findings should be cautiously interpreted and generalized to regions with low-resource settings in Uganda and other sub-Saharan African countries.

V. CONCLUSION

COVID-19 vaccine acceptance rate among the study population was encouragingly high despite misinformation and disinformation in Ugandan media. Participants were more likely to accept COVID-19 vaccines among those who strongly disagree and disagree that vaccines in northern Uganda's health facilities were safe than those who strongly agree; smokers compared to non-smokers, and participants from Gulu, Kitgum, and Pader districts compared to Lamwo district. However, it was less likely for participants with comorbidities to accept COVID-19 vaccines compared to participants without comorbidities. The fear of contracting coronavirus and death if not vaccinated contributed substantially to COVID-19 vaccine acceptance in northern Uganda. There is a need for health managers to engage, sensitize and mobilize the population on COVID-19 vaccines and vaccination using VHTs and other structures, which remain critically important if the high COVID-19 vaccine acceptance rate in the subregion is maintained or improved.

5.1 Statements and Declarations

Ethics approval and consent to participate

The St. Mary's Lacor Hospital Institutional, Review and Ethics Committee approved this study (LHIREC No. 0193/10/2021). In addition, the study was conducted following relevant

institutional guidelines and regulations. Each study participant consented to the study.

Availability of data and materials
All datasets supporting this article's conclusion are within this article and are accessible by a reasonable request to the corresponding author.

Competing interests: All authors declare no conflict of interest.

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Authors' contributions: This study was designed by DLK, JNO, JA, SB, PA, and FWDO. JA, JNO, PA, FWDO, and DLK supervised data collection. ENI and DLK conducted data analysis and interpretation. SB, CO, PA, NOA, DA, JNO, DO, POO, SGO, FPP, ENI, FWDO, JA, and DLK wrote and revised the manuscript. All Authors approved the manuscript and attested they met the ICMJE criteria for authorship.

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Dental Care for Kabuki Syndrome Patient: A Case Report

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ABSTRACT

Oral manifestations accompanying the syndromes may help dentists in diagnosing this syndrome. This article reports the case of a Syrian 4-year-old girl with Kabuki syndrome and the oral/dental aspects of this syndrome; including hypodontia with interdental spacing, abnormal tooth morphology.

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Oral manifestations accompanying the syndromes may help dentists in diagnosing this syndrome. This article reports the case of a Syrian 4-year-old girl with Kabuki syndrome and the oral/dental aspects of this syndrome; including hypodontia with interdental spacing, abnormal tooth morphology.

Keywords: kabuki syndrome, early childhood caries, hypodontia.

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I. INTRODUCTION

Kabuki syndrome (KS) was described in 1981 at two Japanese centers in the Kanto area and Hokkaido [1] [2]. It is a rare genetic disorder (congenital distortion syndrome) [3] which characterized by multiple congenital anomalies and mental disability [4] [5]. Proportion of Kabuki Syndrome is around 1/32,000 of births [3]. The main cause of Kabuki Syndrome is unknown. However, X-linked and autosomal dominant gene have been suggested [6] [7] [8].

Whereas KMT2D (MLL2) gene mutations were observed in most patients with Kabuki Syndrome, and a few have mutation or deletion of KDM6A [3]; thus the first pathogenic gene recognized in Kabuki Syndrome patients was KMT2D according to Ng, S.B., et al., study [9], But nearly in 30% of patients with Kabuki Syndrome, the Potential genetic defects are still unknown [3].

Diagnosis of the syndrome is based on 5 main clinical features: (1) a special face (100%) which characterized by protruding ears, depressed nasal tip and long palpebral fissures with eversion of the lateral third of the lower eyelids, higharched eyebrows with sparse lateral one-third, (2) Growth deficiency (83%) with short stature, (3) moderate to severe mental disability (92%), (4) skeletal anomalies (92%) and (5) abnormalities of dermatoglyphic (93%) [7] [10].

The face of patients with Kabuki syndrome is similar to the makeup worn by actors of Kabuki; a Japanese traditional play. That's why it's called Kabuki syndrome [8].

Other important clinical features have been reported include: early puberty, premature breast development in girls, anal atresia, congenital heart disorder, craniofacial anomalies, gastrointestinal anomalies, fingers abnormalities (Short fifth fingers), dental anomalies, [6] [7] [4] [5] [10] and renal and vertebral anomalies [3].

The most frequent oral manifestations reported were: cleft lip/palate; bifid tongue and uvula; malocclusion (micrognathia, severe maxillary recession, mid-facial hypoplasia, high-arched palate, widely spaced teeth); delayed tooth eruption pattern; dental abnormalities (hypodontia, conical teeth, neonatal teeth, large pulp chamber); diastema and lower lip pits [11] [12] [8].

Other oral manifestations reported in Do Prado Sobral et al., Study are: Developmental Enamel Defects (DED), Dental crowding, Atypical crown shape, Taurodontia, Microdontia, and Retained primary teeth [4].

This article documents the case of a Syrian girl diagnosed with Kabuki syndrome; addressing the clinical features observed, and the dental treatment submitted. Comparing oral manifestations previously described in the literature and those observed in this present case.

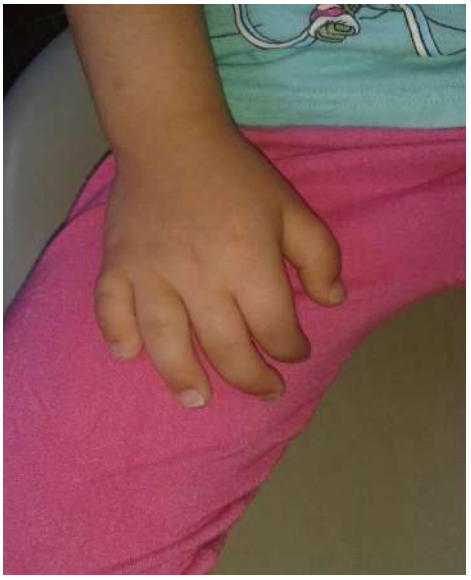

Figure 1: Short Fingers (absence of the third phalanx from the fifth finger)

II. CASE REPORT

A 4-years-old female child diagnosed with Kabuki syndrome by Pediatric Hospital (Damascus University), was referred to the department of pediatric dentistry (Faculty of Dentistry of, Damascus University) for dental care. Chief complaint was the presence of teeth caries. The girl was born to healthy parents after full-term pregnancy and had been diagnosed with Kabuki syndrome. Examination and syndrome diagnosis were done by pediatric specialist and genetic clinic in pediatric hospital and the hospital's report shows stature incompatible with her chronological age; craniosynostosis with Microcephaly. Physical examination shows short fingers (absence of the third phalanx from the fifth finger) (Figure. 1), special facies consisting of narrow front, high-arched eyebrows with scattered lateral one-third, elongated palpebral fissures, eyes with eversion of the lateral one-third of the lower eyelids, small eyeball, prominent ears, broad depressed nasal root with flat nasal tip. (Figure. 2) Anal atresia which was treated surgically within a few days of giving birth delivery.

Figure 2: Special Face Consisting of Narrow Front, High-Arched Eyebrows With Sparse Lateral One-Third, Eyes with Eversion of the Lateral One-Third of the Lower Eyelids, Small Eyeball, Prominent Ears, Broad Depressed Nasal Root With Flat Nasal Tip

The girl showed a noticeable improvement acquired psychomotor skills, she is able to run and go up the stairs, formulate sentences of three words, count until number 5, and Play with dolls. She has a moody and shy behavior.

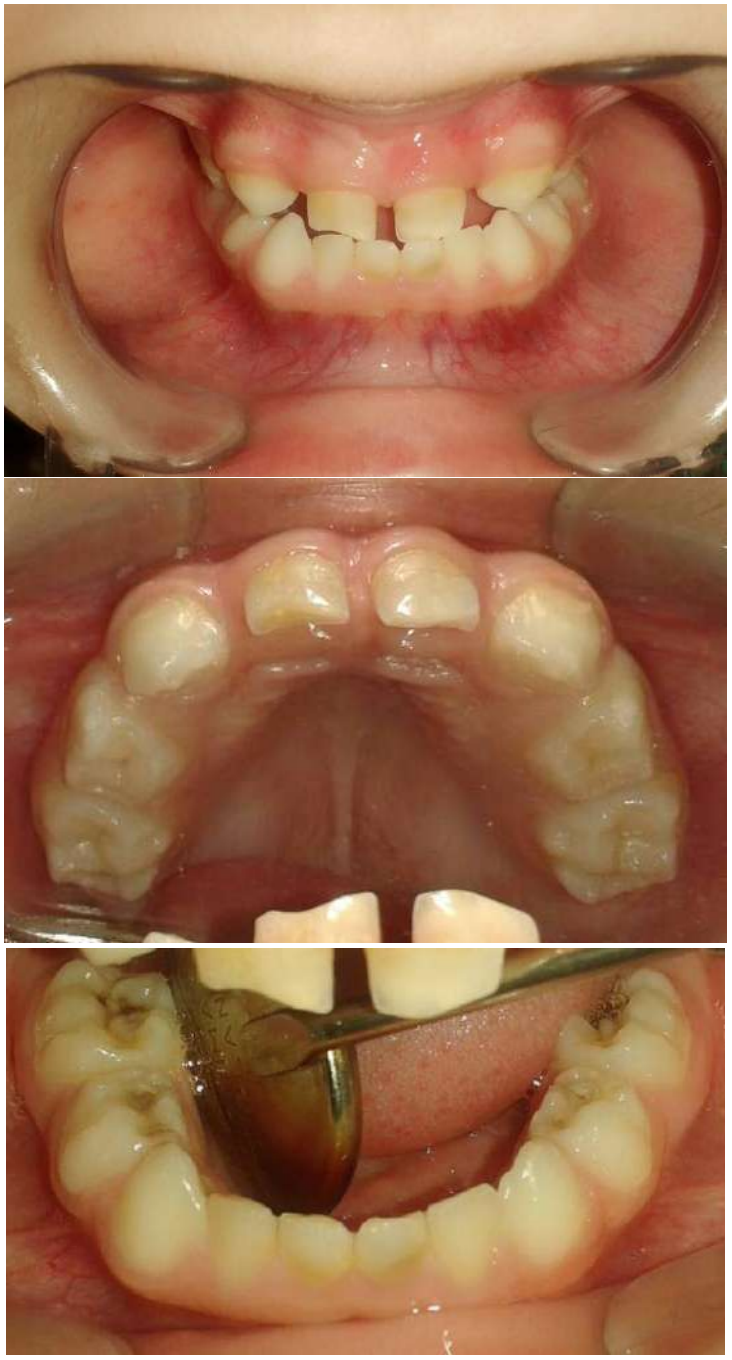

Figure 3: (a) Intra-Oral View of Anterior Teeth, (b) Maxillary Occlusal View, (c) Mandibular Occlusal View

2.1 Intra-Oral Examination

In intraoral examination; no abnormalities were observed in lips, tongue and oral mucosa.

The patient was in primary dentition stage; with edge-to-edge bite, high-arched palate, in the upper arch the present teeth were primary central incisors, primary canines, first and second primary molars, the upper incisors as 'flat head' screwdriver-shaped, in the lower arch the present teeth were primary central and lateral incisors, primary canines, first and second primary molars.

The primary maxillary lateral incisors were absent (hypodontia) with interdental spacing.

Carious cavities were seen in the mandibular first and second primary molars.

2.2 Radiographic Findings

A panoramic photo (Figure. 4) showed carious mandibular second primary molars. The primary maxillary lateral incisors (previously noted as absent), the maxillary permanent lateral incisors buds and mandibular permanent central incisors buds, and the right mandibular permanent lateral incisors buds were absent, while the maxillary permanent second and third molars and the mandibular third molars buds were not considered as absent because they need time to develop.

According to the American Association of Pediatric Dentistry (AAPD), this case is classified as Early Childhood Caries (ECC) [13].

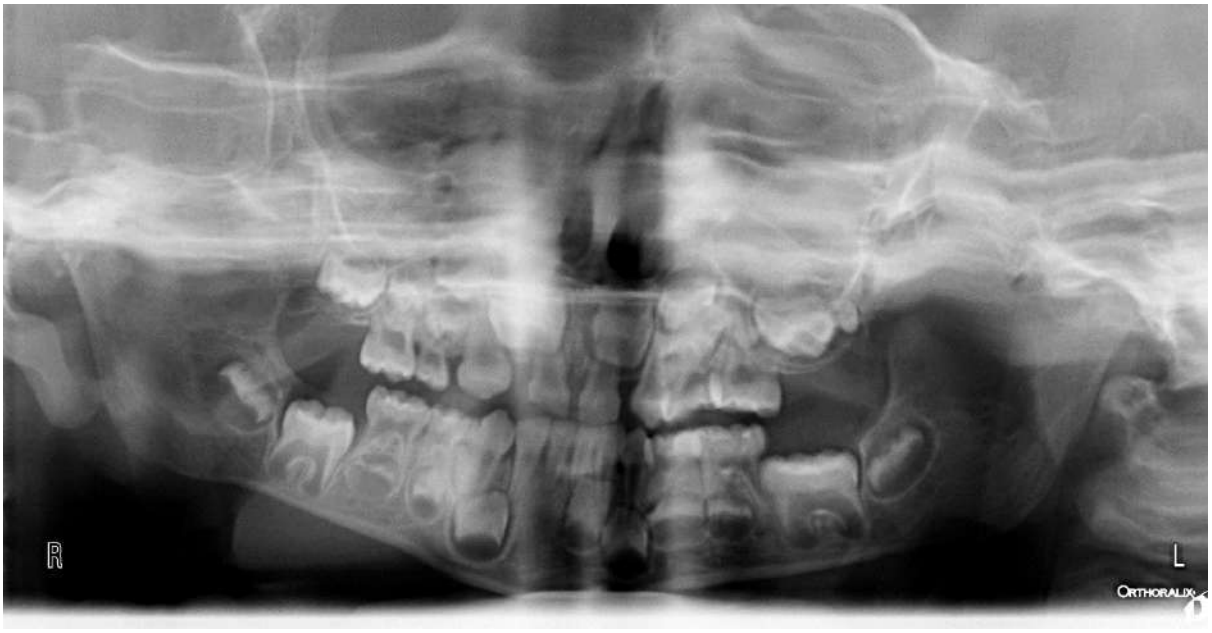

Figure 4: Panoramic Photo

2.3 Treatment

The girl's behavior was Negative (Reluctance to accept treatment, uncooperativeness, some evidence of negative attitude but not pronounced (sullen, withdrawn) according to the Frankl behavior rating scale [14].

The dental treatment was accomplished under intravenous sedation (one session) by an anesthesiologist in the oral and maxillofacial surgery hospital, Damascus University.

Whereas a medical specialist consultation for sedation had been requested, and pre-sedation dietary instructions which determined by the American Academy of Pediatric Dentistry had been given: (1). Clear liquids: up to 2 hours before the procedure. (2). Breast milk up to 4 hours before the procedure. (3). Infant formula, nonhuman milk or a light meal up to 6 hours before the procedure [15]. And the medication used in IV sedation was (Midazolam 1.5 mg, Fentanyl, 7 Microgram and Propofol 30 Mg) (girl weighed 15 kilograms), while the treatment session lasted 45 minutes. Dental treatment included:

- Pulpotomy of the left primary second mandibular molar and applying of Stainless-steel crown (SSC).
- Restoration of the right and left primary first mandibular molars with amalgam.
- Hall Technique on right primary second mandibular molar.
- Sealing of the left and right primary maxillary molars.
- Parent was given oral hygiene instruction.

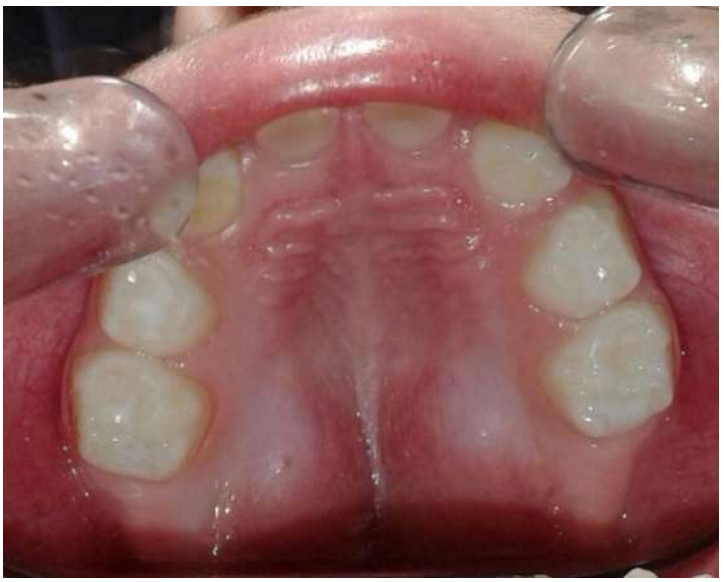

Figure 5: Maxillary Occlusal View after Treatment

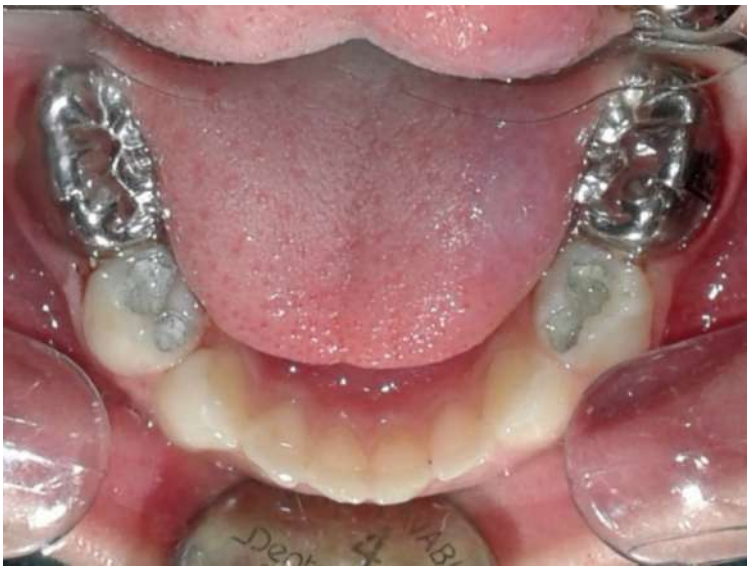

Figure 6: Mandibular Occlusal View after Treatment

IV. DISCUSSION

Kabuki syndrome is considered as a rare condition; although dentists may find difficult to understand the case, but they may contribute to the diagnosis, so it is important to know the facial and oral clinical manifestations accompanying this syndrome to request further examinations when noticing any changes in the normal state.

The etiology of the Syndrome is unclear, and diagnosis is clinically and mainly based on facial features in addition to other clinical features: Growth deficiency, mental disability, skeletal anomalies, abnormalities of dermatoglyphic [4].

Typical facial features can be identified from an early age to help in clinical diagnosis. However; clinical identification of the syndrome in the neonate is difficult, maybe the phenotype is developed by the time [12].

The patient in this case has a short stature, craniosynostosis with Microcephaly, short finger, special facies consisting of narrow Front, high-arched eyebrows with sparse lateral one-third, elongated palpebral fissures, eyes with eversion of the lateral one-third of the lower eyelids, Small eyeball, prominent ears, broad depressed nasal root with flat nasal tip. These manifestations also reported by Petzold et al.,

2003, Lung and Rennie, 2006, Dos Santos et al., 2006, Cudzilo and Czochrowska, 2018, Shangguan et al., 2019, and Santos et al., 2019 [16], [12], [17], [18], [10], [19].

Dental abnormalities have been reported in over 60% of patients with Kabuki Syndrome [11] [17] [20]. The most common dental finding was the hypodontia [8], in this case Maxillary primary lateral incisors, the maxillary permanent lateral incisors buds, mandibular permanent central incisors buds, and the right mandibular permanent lateral incisors buds were absent, these findings about missing teeth are in agreement with the literature reported by Mhanni et al., Matsune et al., Petzold et al., Lung and Rennie, dos Santos et al., Teixeira et al., and Tuna et al., [21], [11], [16], [12], [17], [8], [20]. The finding of absent premolars or molars as described by Mhanni et al., Tuna et al., and do Prado Sobral et al., were not observed [21], [20], [4].

Space between maxillary teeth that was found in this case is associated with hypodontia, and this characteristic was reported previously by Petzold et al., [16], in addition to the high-arched palate which also observed by Matsune et al., and do Prado Sobral et al., [11], [4].

The upper incisors were as 'flat head' screwdriver-shaped, this finding was reported by Mhanni et al., Petzold et al., Lung and Rennie, Do Prado Sobral et al., and Cudzilo and Czochrowska [21], [16], [12], [4], [18], whereas Dental shape abnormalities were not observed in Teixeira et al., who study dental examination and panoramic radiography of nine patients [8]. There are no lips, oral mucosa or tongue abnormalities observed in this present case.

Pediatric dentists should choose the best behavioral management technique that fit the patient status as well as the procedure nature which needs to be accomplished, and they have often found that anxiety and behavioral assessment to be helpful in determining the behavioral management technique to be chosen for each child [15].

Sedation requires an accurate medical history accomplishment to determine whether the patient a good candidate to it or not. The American Society of Anesthesiologists (ASA) guidelines are considered as the most accurate method when taking patients medical history [15], and case in this report is classified as ASA class II that is frequently considered appropriate candidate for minimal, moderate, or deep sedation. However, counsel with an anesthesiologist is often desired [15].

While IV Sedation can be a suitable alternative to general anesthesia for children with ECC and the equipment to provide general anesthesia is far more expensive than what is required for IV sedation [22], in addition to the girl's behavior in this case was negative according to the Frankl behavior rating scale [14] as well as the treatments were required enough time to be accomplished, therefore dental treatment in this case was done under intravenous sedation.

V. CONCLUSIONS

The dental manifestations observed in this case were hypodontia, abnormal teeth morphology and high-arched palate.

These dental abnormalities in addition to another clinical features may help in the clinical diagnosis of the syndrome, so It is important that dentist be aware of this syndrome and its facial manifestations and oral/dental findings to recognize children who may be affected by this disorder.

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Characteristics of Obstetric Violence in Brazil: The Urgency Need to Implement Health Policies

Mariana Francisca da Silva, Tawana de Araújo Leite Freitas Do Ó, Ednaldo Antônio da Silva, Claudeny Barbosa Spinelli, Edivaldo Rosa Alves, José Ronaldo de Lima, Erika Becker Figueirêdo Madeira & Josinês Barbosa Rabelo

ABSTRACT

Introduction: Obstetric Violence is defined as violence committed against women in any period of pregnancy. It can be sexual, physical, psychic and verbal, in addition to negligence, discrimination and/or unnecessary interventionist conduct.

Objetive: To characterize the types of Obstetric Violence in Brazil.

Method: Integrative review of queries in the databases: BVS, PubMed, Medline and Lilacs from January 2017 to September 2022. Descriptors were used individually or combined. N=518 publications were retrieved, after exhaustive reading of the titles and abstracts of the articles, n=460 articles on the subject published in full and available free of charge were selected. After applying the inclusion and exclusion criteria, n=118 studies were selected to be read in full. After these procedures, n=05 papers were selected with a focus on answering the guiding question, on adapting the content used to support the structuring of this integrative review.

Keywords: obstetric violence; childbirth; obstetric nurses, nurse-patient relations.

Classification: NLM Code: WQ 330

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Characteristics of Obstetric Violence in Brazil: The Urgency Need to Implement Health Policies

Características da Violência Obstétrica no Brasil: A Urgência Necessidade de Implementação de Políticas de Saúde

Mariana Francisca da Silva[α], Tawana de Araújo Leite Freitas Do Ó[σ], Ednaldo Antônio da Silva[ρ], Claudeny Barbosa Spinelli[CD], Edivaldo Rosa Alves[¥], José Ronaldo de Lima[§], Erika Becker Figueirêdo Madeira[χ] & Josinês Barbosa Rabelo[v]

RESUMO

Introdução: A Violência Obstétrica é definida como aquela cometida contra mulheres em qualquer período da gestação. Ela pode ser sexual, física, psíquica e verbal, ademais a negligência, discriminação e/ou as condutas intervencionistas desnecessárias.

Objetivo: Caracterizar os tipos de Violência Obstétrica no Brasil.

Método: Revisão Integrativa de consultas nas bases de dados: BVS, PubMed, Medline e Lilacs no período de Janeiro de 2017 a Setembro de 2022. Os Descritores foram utilizados individualmente ou combinados. Foram resgatados n=518 publicações, após leitura exaustiva dos títulos e resumos dos artigos, selecionaram-se n=460 artigos sobre a temática publicados completos e disponíveis gratuitos. Após aplicação dos critérios de inclusão e de exclusão, n=118 estudos foram selecionados para serem lidos na íntegra. Após esses procedimentos, selecionou-se n=05 trabalhos com enfoque na resposta à questão norteadora, na adequação do conteúdo empregado para subsidiar a estruturação desta revisão integrativa.

Resultados: Os estudos analisados estão hospedados em revistas de grande relevância científica elaboradas por pesquisadores de reconhecimento nacional e internacional que orientam a tomada de decisões e elaboração de políticas públicas aos estados membros da ONU. A VO apresenta características física, psicológica, sexual, moral e institucional; Mesmo assegurado na Constituição Federal, os dados apontam a inexistência de um marco regulatório específico para mitigar a Violência Obstétrica no Brasil.

Conclusões: A Violência Obstétrica é resultante das desigualdades de gênero: tem sexo e idade (20 a 34 anos), tem cor/raça (negra, parda e indígena) tem classe social (pobre e classe média baixa), tem escolaridade (analfabetas, semi analfabetas, e com baixa escolaridade). Tem endereço (residentes das regiões - norte e nordeste; habitantes de guetos e favelas); Apresenta características física, psicológica, sexual, moral e institucional. É papel da enfermagem obstétrica prevenir, denunciar e promover ações estratégicas de combate a violência, bem como a urgência da necessidade da criação de manual operacional para prevenção e condutas na ocorrência da VO e a tipificação dessa violência por parte do legislativo. É importante que a Rede de Proteção, Defesa e Apoio funcione interligada e articulada com a Clínica Ampliada.

Palavras-Chaves: Violência Obstétrica; Parto; Enfermeiras Obstétricas, Relações Enfermeiro-Paciente.

ABSTRACT

Introduction: Obstetric Violence is defined as violence committed against women in any period of pregnancy. It can be sexual, physical, psychic

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and verbal, in addition to negligence, discrimination and/or unnecessary interventionist conduct.

Objetive: To characterize the types of Obstetric Violence in Brazil.

Method: Integrative review of queries in the databases: BVS, PubMed, Medline and Lilacs from January 2017 to September 2022. Descriptors were used individually or combined. N=518 publications were retrieved, after exhaustive reading of the titles and abstracts of the articles, n=460 articles on the subject published in full and available free of charge were selected. After applying the inclusion and exclusion criteria, n=118 studies were selected to be read in full. After these procedures, n=05 papers were selected with a focus on answering the guiding question, on adapting the content used to support the structuring of this integrative review.

Results: The analyzed studies are hosted in journals of great scientific relevance prepared by researchers of national and international recognition who guide the decision-making and elaboration of public policies to UN member states. VO presents physical, psychological, sexual, moral and institutional characteristics; Even guaranteed in the Federal Constitution, data point to the lack of a specific regulatory framework to mitigate Obstetric Violence in Brazil.

Conclusions: Obstetric Violence results from gender inequalities: there is gender and age (20 to 34 years), color/race (black, brown and indigenous) social class (poor and lower middle class), schooling (illiterate, semi-illiterate, and with low schooling). It has an address (residents of the regions - north and northeast; inhabitants of ghettos and slums); It presents physical, psychological, sexual, moral and institutional characteristics. It is the role of obstetric nursing to prevent, denounce and promote strategic actions to combat violence, as well as the urgency of the need to create an operational manual for prevention and conduct in the occurrence of OV and the typification of this violence by the legislature. It is important that the Protection, Defense and Support Network works interconnected and articulated with the Extended Clinic.

Keywords: obstetric violence; childbirth; obstetric nurses, nurse-patient relations.

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I. INTRODUÇÃO

A Violência Obstétrica (VO) é definida como aquela cometida pelos profissionais de saúde contra mulheres em qualquer período da gestação, no pré-natal, no pré-parto, no parto, no pós-parto e no atendimento ao aborto, sendo caracterizada como uma forma específica de violência de gênero (SAUAIA; SERRA, 2016; COFEN, 2019).

A VO é definida como a apropriação do corpo e dos processos reprodutivos da mulher pelos trabalhadores de saúde, mediante tratamento desumanizado, abusa de medicalização e patologização dos processos naturais, que acabam resultando na perda de autonomia da gestante e de sua capacidade de decidir de maneira livre sobre seu corpo e sua sexualidade. Inclui a violência por negligência, que ocorre por meio da negativa de atendimento ou das imposições de obstáculos ao cumprimento dos direitos das gestantes (OMS, 2002). Cujas consequências repercutem no período pós-gestação (SILVA et al., 2022).

Minayo & Assis (1993) apontam que em qualquer ação para superar as desigualdades, miséria e a violência passa por articulação intersetorial, interdisciplinar, multiprofissional e com organizações da sociedade civil e comunitária que militam por direitos e cidadania. Para Pnud (2012), o contexto democrático brasileiro não é vivenciado com a mesma intensidade por todas as pessoas, de modo que, parte dos segmentos sociais não participam na mesma condição de acesso aos direitos e vivências proporcionados pela sociedade.

Desse modo, a violência obstétrica é fruto das desigualdades resultantes dos diversos processos sociais e culturais que afetam diretamente e diferentemente as mulheres dos setores de menor poder aquisitivo tornando com isso, um problema de ordem nacional, caracterizando-se como uma questão de saúde pública e justiça. Assim, os abusadores não são responsabilizados, atribuindo a dor e o sofrimento no parto como culpa da mulher, da família ou da classe social onde ela vive. Provocando prejuízos sociais para as mulheres, crianças, famílias e sociedade, a ocorrência da VO expõe a fragilidade do Estado em não conseguir responsabilizar ou preveni-la. Por isso, existe a necessidade de conhecer os tipos e as características da VO, tendo como resultados os fatores externos. Como também, oferecer informações científicas para apoiar uma recomendação aos profissionais de saúde e sociedade, no sentido de subsidiar a tomada de decisões e elaboração de medidas para reduzir e evitar novos casos (JARDIM; MODENA, 2018). Nesse cenário traçamos como *Objetivo Geral:* Caracterizar os tipos de Violência Obstétrica no Brasil.

II. MÉTODO

Este estudo trata-se de uma Revisão Integrativa da literatura que tem por finalidade agrupar e sintetizar resultados de pesquisas empíricas sobre o tema em questão. Assim, foi utilizada a estratégia PICO para elaboração da pergunta norteadora: Quais os tipos e as características da Violência Obstétrica no Brasil, no sentido de subsidiar os profissionais de saúde em sua atuação diante dessa ocorrência?

A busca e a seleção de artigos ocorreram no período de 05 anos (01 janeiro de 2017 a 01 outubro de 2022) por meio do acesso às bases de dados: MEDLINE (*Medical Literature Analysis and Retrieval System Online*/PubMed (*National Institutes of Health's National Library of Medicin*e (NIH/NLM)), BVS (Biblioteca Virtual em Saúde); Literatura Latina Americana em Ciências de Saúde (LILACS) e (BDENF – ENFERMAGEM).

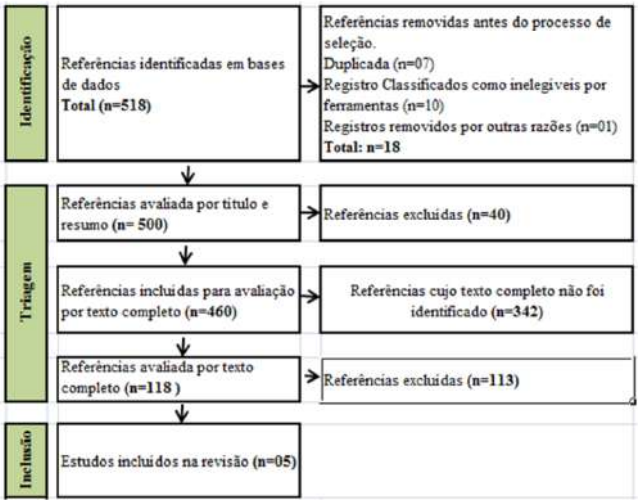
Para cada portal de pesquisa foi elaborada uma estratégia específica de cruzamento dos Descritores em Ciências em Saúde (DeCS), base brasileira de palavras-chave médicas ou do *Medical Subject Headings* (MeSH). Os Descritores de Saúde (DeCS) utilizados para selecionar os estudos foram: Violência Obstétrica; Parto, Enfermeiras Obstétricas, Relações Enfermeiro-Paciente e as suas respectivas terminologias no *Medical Subject Headings* (MeSH): *Obstetric Violence; Parturition; Nurse Midwives; Nurse-Patient Relations*.

Os operadores booleanos "*AND*" e "*OR*" foram usados para combinar palavras-chave e termos para as buscas das publicações.

A busca realizada teve como período, os artigos publicados nos últimos 05 anos (2017-2022). A pesquisa foi desenvolvida de 01 de março a 30 de setembro de 2022. Pelo acúmulo de arcabouço teórico sobre o tema. Partindo-se da leitura na ordem de título, resumo e texto integral, selecionaram-se os artigos por meio da metodologia *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*-PRISMA (MOHER, 2009).

A partir da busca inicial nas plataformas mencionadas, foram resgatados n=518 publicações, após leitura exaustiva dos títulos e resumos dos artigos, selecionaram-se n=460 artigos sobre a temática, publicados completos e disponíveis e gratuitos. Após aplicação dos critérios de inclusão e de exclusão, n=118 estudos foram selecionados para serem lidos na íntegra. Após esses procedimentos, selecionou-se n=05 trabalhos com enfoque na resposta à questão norteadora, na adequação do conteúdo empregado para subsidiar a estruturação desta revisão integrativa.

Figura 01: Fluxograma do processo de identificação, seleção e inclusão das publicações que compuseram a revisão integrativa, elaborado a partir da recomendação PRISMA na bases de dados *PubMed, SciELO, BVS (Bireme/LILACS), BENF*



Fonte: Feito pelos autores em 2023 (PRISMA, 2021)

Com a finalidade de sintetizar as informações da interpretação das n=05 publicações elegíveis, procedeu-se à elaboração de quadros contendo: autores do estudo, ano da publicação, objetivo, método, resultados. A sumarização otimizou o processo de extração dos dados e a análise das produções científicas referentes às características e tipificação da VO.

III. RESULTADOS

O corpus de análise é composto de n=05 artigos publicados em: 2018 (n=01); 2019 (n=02); 2020 (n=01); 2022 n=01). Estão publicados em n=04 Revistas de abrangência nacional e internacional: Sendo das regiões, cidades com alto índice populacional no Brasil - América do Sul; Itália -

Europa; Estados Unidos da América - América do Norte. Dos quais, 60% (n=03) estão publicados em Português e 40% (n=02) em Inglês.

Os autores são profissionais de distintas áreas de formação, (100%) são graduados, 50% são mestres, 50% doutores, e em menor número são pós- doutorados. São pesquisadores, consultores e membros de agências e instituições nacionais e internacionais de grande relevância científica, como a ONU, OMS, Ministério da Saúde, Fiocruz e Abrasco. Possibilita assim, relevância clínica ampliada.

Quadro 01: Síntese das Publicações Utilizadas Nesta Revisão

Autor, Ano	Categorias	Descrição
SILVA, Rafaela Camila Freitas da et al., 2018	Objetivo	Compreender a satisfação das mulheres durante o parto normal.
	Método	Estudo qualitativo, exploratório e descritivo, a partir de entrevistas com vinte mulheres, residentes no interior de São Paulo. O Interacionismo Simbólico e a Análise de Conteúdo Temática sustentam este estudo.
	Resultados	A satisfação foi correlacionada com efetivação do desejo de parir, suporte acolhedor de doulas/profissionais de saúde e presença de acompanhante/familiares no processo, mas também revela partos marcados por vivências invasivas, impositivas e não acolhedoras.
LANSKY Sônia et al. 2019	Objetivo	Analisar o perfil e a experiência de parto de 555 mulheres que visitaram a exposição durante a gestação, com enfoque na percepção sobre Violência Obstétrica.
	Método	Estudo transversal multicêntrico e multimétodos com componente quantitativo e qualitativo, integrante da pesquisa Sentidos do Nascer. Realizada Entrevista com 555 mulheres
	Resultados	Predominaram: intervenção não consentida/aceita com informações parciais, cuidado indigno/abuso verbal; abuso físico; cuidado não confidencial/privativo e discriminação. Ações educativas previne a VO,
ZAAMY, Sônia et al. 2019	Objetivo	Descobrir se a episiotomia, procedimento invasivo amplamente aplicado, pode constituir fator determinante de responsabilização dos profissionais de acordo com as normas de Violência Obstétrica.
	Método	Pesquisa Documental de leis e documentos, declarações e observações de organizações internacionais de saúde.
	Resultados	Em 34% dos partos não há razões explicadas para a realização de uma episiotomia. 54% das mulheres nunca deram permissão e 51% nunca recebeu anestesia local. É frequente observar em salas obstétricas mulheres seminuas na presença de estranhos, ou sozinhas em ambientes hostis, em posições, de submissão total, com abertura e pernas levantadas e com órgãos genitais expostos, e mães separadas de seus filhos logo após o nascimento. Realização de cesarianas desnecessárias; privação de alimentos e a possibilidade de se locomover; rotina e exames vaginais repetitivos sem justificativa; uso frequente de ocitocina para agilizar o trabalho de parto; episiotomia sem consentimento e manobra de Kristeller.
ZAMPAS, Cristina et al. 2020	Objetivo	Desvendar os motivos dos maus-tratos de mulheres durante o parto e como eles são entendidos e abordados dentro Direitos Humanos
	Método	As mulheres têm direito a cuidados de saúde dignos e respeitosos, livres de discriminação e coerção, durante a gravidez e o parto, conforme leis e normas internacionais de Direitos Humanos.
	Resultados	É importante o uso abordagem baseada em Direitos Humanos para mitigar os maus-tratos e acelerar a cobertura universal de saúde.

LEITE, Tatiana Henriques et al. 2022	Objetivo	Discutir e refletir sobre como as questões relacionadas à definição e terminologia, mensuração e políticas públicas no Brasil têm dificultado a pesquisa da temática, assim como a mitigação desses atos.
	Método	Pesquisa Documental em de leis e documentações emitidas sobre o assunto.
	Resultados	As ausências de estudos causais afetam a tomada de decisão em saúde, prejudicando a elaboração de políticas públicas específicas

Fonte: Elaborado Pelos Autores, a Partir das Plataformas PubMed, BVS BIREME

Observou-se que, o Ministério da Saúde (MS) brasileiro, por meio do *Despacho SEI/MS – 9087621* de 03 de maio de 2019, recomendou a restrição do uso do termo Violência Obstétrica em documentos oficiais, relatórios, pareceres e estudos. Para Reis (2019), a restrição tem valor simbólico negativo por interditar o discurso dos diversos atores, como pesquisadores, gestores, usuários e profissionais de saúde. Excluir o uso do termo pode soar como censura institucional. Para Cancian (2019), o ideal é discutir porque esse incômodo é tão grande e esclarecer que não é dirigido a ninguém em específico, mas à situação da VO, uma violência estrutural. Somado a isso, a pandemia da COVID-19 pode ter contribuído para a redução de pesquisas referente a temática deste estudo em 2020, 2021, 2022.

Quanto ao tipo das Revistas, dois (n=02) estudos (os Artigos: 01 e 03) estão hospedados na Revista Ciência & Saúde Coletiva da Associação Brasileira de Saúde Coletiva (ABRASCO). De categoria A3 no Qualis/Capes. Em 2020 alcançou o Fator de Impacto de IF = 1.336 conforme métrica do *Journal Citation Reports* (JCR) e em 2021, alcançou o Indicador Biométrico de Citação *SJR* Q2: 0,57. Está em 1º lugar no *ranking* do *Google Acadêmico* dentre todos os periódicos científicos brasileiros de qualquer área. Encontra-se indexada em 23 plataformas de busca regionais e internacionais como a *MEDLINE/Index Medicus*, *SCIELO, LILACS, SCOPUS* entre outras. A revista recebe em média acima de 3500 artigos por ano.
Um (n=01) estudo (Artigo: 04) está hospedado na Revista Gaúcha de Enfermagem (RGE) do curso de Pós-Graduação da Escola de Enfermagem da Universidade Federal do Rio Grande do Sul (UFRGS). Tem o objetivo de divulgar produções científicas no campo da Enfermagem. Classificada no estrato A2 Internacional do Qualis-Periódicos. Em 2021 alcançou o Fator de Impacto de IF = 0.638. Encontra-se indexada em 16 plataformas de busca regionais e internacionais como a *MEDLINE/PubMed*, *SCIELO, LILACS, SCOPUS,* BDENF (Base de Dados de Enfermagem), BVS Enfermagem (Biblioteca Virtual em Saúde - Enfermagem) entre outras. A RGE, realiza a avaliação da similaridade textual, utilizando ferramentas para detecção de similaridade (*Software Ithenticate*), aceitando-se o limite de 30% dessa.

Um (n=01) estudo (artigo 02) está hospedado na *Revista European Review for Medical and Pharmacological Sciences* é uma revista médica revisada por pares, da área da farmacologia e farmácia e com 97 subáreas dos diversos campos das ciências da saúde, sociais, humanas com psicologia, ciências médicas, pedagogia, medicina, biologia, fisioterapia, nutrição etc. Com atuação em diversos campos de atuação como Telemedicina, imunologia, diabetes, sociologia médica, obstetrícia etc. Com objetivo de incentivar discussões interdisciplinares e contribuir para o avanço da medicina. É indexado e abstraído em C*urrent Contents, Excerpta Medica, Index Medicus, MEDLINE/PubMed, Science Citation Index e Scopus*.Apresentou Fator de Impacto em 2021: IF = 3.784 e em 05 anos um Fator de Impacto de IF= 3.477, conforme ISI *Journal Citation Reports® Ranking*.

Um (n=01) estudo (Artigo:05) encontra-se hospedado na *Health and Human Rights (HHR)*, um periódico do Centro *François-Xavier Bagnoud* de Saúde e Direitos Humanos da *Harvard School of Public Health,* Boston/MA - Estados Unidos. Tendo como área de abrangência em Direitos Humanos, Bioética; Índice Medicus, Política de Saúde, Promoção da Saúde, Direitos Humanos, Saúde Pública. Apresenta Fator de Impacto em junho de 2022: IF= 2,28 . Encontra-se indexado para *MEDLINE/PubMed*e no *Directory of Open Access Journals*.

Em relação ao perfil dos autores, nos (n=05) estudos são composto de n=32 pessoas, sendo na grande maioria (n=28) pesquisadoras e menor parte (n=04) pesquisadores.

Quadro 02: Perfil dos Autores Segundo Sexo

Artigos	Sexo		Total de Autor
	Feminino	Homem	
Artigo 01	n=07	n=01	n=08
Artigo 02	n=03	n=02	n=05
Artigo: 03	n=06	n=0	n=06
Artigo: 04	n=06	n=0	n=06
Artigo: 05	n=06	n=01	n=07
Total	n=28	n=04	n=32

Fonte: Elaborado Pelos Autores (2023).

Alguns autores atuam como professor, enfermeiros, médicos, diretor, Associado de Advocacia Global no Centro de Direitos Reprodutivos, Nova York; ex-consultor da OMS; no Tribunal Europeu dos Direitos do Homem e na ONU, Conselheira de Direitos da Mulher no Escritório ACNUDH; pesquisadores na Fiocruz; Editor Chefe de Revista científica; Membro do Comitê de Pesquisa do CNPq; membros da Associação Brasileira de Saúde Coletiva (ABRASCO).

IV. DISCUSSÃO

4.1 Tipos E as Características Da Violência Obstétrica

Os estudos apontam que VO são resultantes das desigualdades econômicas, do abismo educacional, da polarização política, do negacionismo e do fim de ideias de bem comum e igualdade. Assim, as mulheres pretas, pobres, descendentes dos povos indígenas, residentes nas periferias, florestas, zona rural são as que mais sofrem com a Violência Obstétrica (VO) nas unidades de saúde pública (SILVA et al., 2018; LANSKY et al., 2019; ZAAMY et al., 2019; ZAMPAS et al., 2020; LEITE et al., 2022). Desse modo, o trabalho de caracterizar os tipos de VO, dá uma dimensão do problema e aponta diretrizes para a tomada de decisões e para a elaboração de políticas públicas. Alguns autores (LANSKY et al. 2019) consideram a VO como uma violência de gênero, por se dirigir especificamente às mulheres e permear relações de poder desiguais em nossa sociedade.

Com esse cenário que a VO se sustenta e se firma como uma violência estrutural por surgir como um conjunto de práticas, hábitos, situações e falas presentes entre os profissionais de saúde que promovem, mesmo sem a intenção, a VO. Tipificar e caracterizar a Violência Obstétrica fomenta um amplo debate sobre essa injustiça tornando com isso um ato de conscientização e prevenção. Mobiliza a comunidade científica em torno de ações afirmativas para combater a VO (SOUZA et al., 2021).

De modo a reapropriar o corpo político da mulher, ampliar o olhar e estabelecer novas intersubjetividades. Desse modo, alguns autores (LANSKY et al., 2019; ZAAMY et al., 2019; LEITE et al., 2022; SILVA et al., 2018; ZAMPAS et al., 2020) tipificam a VO, como violência física, violência psicológica, violência verbal, violência moral (calúnia, injúria ou difamação), violência sexual (OLIVEIRA; ALBUQUERQUE, 2018) e violência institucional (negligência, tempo de espera até ser atendida, exposição no trabalho de parto, não participação nas tomadas de decisões e estrutura inadequada) (SOUZA et al., 2016; CARDOSO et al., 2017), no sentido de fortalecer a democracia em favor da mulher, sobretudo diante dos desafios impostos pela atualidade (LEITE et al., 2022).

Nessa perspectiva, Oliveira & Albuquerque (2018), apresentam as características VO conforme os tipos: violência física, com ações que causem dor (exame de toque para a verificação da dilatação do períneo, quando ocorrida para fins didáticos aos estudantes da área da saúde);

violência psicológica e verbal, como a discriminação: *Tinha que ser! Olha aí, pobre, preta, tatuada e drogada! Isso não é eclampsia, é uma droga*!; violência sexual: com a adoação de práticas desnecessárias para o momento, como a episiotomia. Prática conceituada, inclusive, por alguns estudiosos, como mutilação genital feminina, dentre outras formas (OLIVEIRA; ALBUQUERQUE, 2018).

No Brasil, a pesquisa *"Mulheres brasileiras e gênero nos espaços públicos e privados"*, realizou estudo com 23.894 mulheres das regiões Norte, Nordeste e Centro-Oeste, os dados apontam que uma (n=01) em cada quatro (n=04) mulheres sofrem algum tipo de VO (física, verbal, moral, psicológica) durante o parto, procedimentos dolorosos sem consentimento ou informação, falta de analgesia, gritos, falta de confidencialidade, o profissional abusa do poder, discriminação, falta de comprometimento, ameaça, constrangimento, humilhação, manipulação, proibições e até negligência (LEAL et al., 2014).

Na pesquisa *Nascer no Brasil*, o inquérito nacional, com 15.688 mulheres, realizado nas regiões Norte, Nordeste e Centro-oeste, apontou excesso de intervenções no parto e nascimento, assistência marcada por intervenções desnecessárias, prejudiciais, expondo mulheres e crianças a iatrogenias. Constatou-se maior ocorrência da VO verbal, física ou psicológica para as mulheres de baixo nível sócio-econômico, de minorias étnicas (pardas e/ou pretas), baixa escolaridade, adolescentes e mulheres solteiras, com idade entre 20 e 34 anos, prevalência das regiões Norte e Nordeste, migrantes, com parto por via vaginal, que não tiveram acompanhante durante a internação, atendidas no setor público (D'ORSI et al., 2014) e as as que vivem com HIV (OMS, 2014).

Para Leite et al. (2022), os maus-tratos vivenciados pelas mulheres no momento do parto, a ausência de estudos causais afeta a tomada de decisão em saúde, prejudicando a elaboração de políticas públicas específicas. Nessa definição, a violência é descrita como "atos de natureza intencional com potencial de causar danos", associando a intencionalidade ao próprio ato de violência, independentemente do resultado que o mesmo produz. Componente importante, uma vez que independe da equipe de saúde, sendo considerada uma Violência Obstétrica Institucional.

D'Oliveira, Dini&, Schraiber (2002) conceituam Violencia Obstétrica Institucional como tipo de violência de gênero no parto e aborto. Caracterizada como a oferta de uma estrutura inadequada (tem potencial para ferir a dignidade e a privacidade da mulher) e reduz a capacidade do hospital/maternidade em ofertar o melhor atendimento possível, considerando as evidências científicas, relativo a isso, a mulher pode apresentar depressão pós-parto (SOUZA, 2014).

Outro estudo aponta que violência institucional acontece mais frequentemente em serviços públicos (GUIMARÃES; JONAS; AMARAL, 2018).

Silva et al. (2018) caracterizam a VO como os partos marcados por experiências invasivas, impositivas e pouco acolhedoras. Assim, as evidências do estudo da pesquisa de Zampas et al. (2020) indicam que pouco mais de 30% da população sofreu maus-tratos durante o parto em unidades de saúde e as mulheres correm um risco maior de sofrer abuso físico e verbal entre 30 minutos antes do nascimento até 15 minutos após o parto.

Os resultados da análise de Santos et al. (2022) obtidos na aplicação de questionário a 96 parturientes do Estado do Pará, na região Norte do país, apontou, que a intervenção de manter a mulher em jejum, foi relatada por 62,5% das parturientes. Resultados parecidos, também foram encontrados na análise de Rodrigues et al. (2017) que entrevistaram 3.765 puérperas provenientes do estado do Ceará, da região Nordeste do Brasil, os dados evidenciam que não foi ofertado a ingesta hídrica a 70,8% e a alimentação a 77,3% das parturientes. Pode ser observado que mesmo com as orientações da OMS (OMS, 2014) sobre as condutas que deverão ser adotadas e implementadas no trabalho de parto ainda está distante de uma aplicabilidade

dentro das instituições obstétricas. Estes dados remetem a um questionamento: o que estaria dificultando a não aplicação das novas evidências científicas a essas gestantes?

Nesse contexto, Carvalho et al. (2018), apontam que a VO pode ser compreendida como qualquer ação que produza efeitos negativos de caráter físico e psicológico durante o processo parturitivo natural, e sua materialização ocorre por meio de um tratamento desumanizado oriundo dos profissionais de saúde.

A VO é um fator de risco para o desenvolvimento de Transtorno de Estresse Pós-Traumático (TEPT), quadro ansiosos e depressão pós-parto e pensamentos suicidas (KHSIM et al., 2022; LEPAZPI et al., 2022). VO Psicológica se apresenta diante da pressão vivenciada pela mulher no momento do parto. Causando diminuição da autoestima, dano emocional, sofrimento psíquico e angústia intensificada pelo medo e pela insegurança, provocado pela sensação de inferioridade através da humilhação, controle das vontades da parturiente que reforçam a crença de incapacidade e impotência de seu corpo (OLIVEIRA; ALBUQUERQUE, 2018).

Com isso, a mulher pode desenvolver traumas marcados pelos esquemas de vulnerabilidade, privação emocional, defectividade, autocontrole insuficiente e subjugação ao ponto de evitar uma nova gestação e evoluir ao quadro de depressão pós-parto (SOUZA, 2014; ZANARDO et al., 2017). Entretanto, há uma naturalização da VO, pois o desconhecimento e o silêncio das mulheres diante da VO, mostrou-se algumas vezes como “aceitável” e “normal” (OLIVEIRA; ALBUQUE-RQUE, 2018).

Nesse debate, Oliveira & Albuquerque (2018), também caracterizam a VO verbal com palavras inadequadas, constrangendo a parturiente, inferiorizando ou humilhando por sua condição pessoal, e pelas suas escolhas feitas no momento do parto, onde desrespeita a sua integridade. Desse modo, a Fundação Perseu Abramo (FPA, 2013) apresenta algumas situações de Violência Obstétrica:

> Impedir que a mulher tenha um acompanhante, exigir que este acompanhante seja uma mulher ou restringir os horários de acompanhamento. [...] Condicionar a presença do acompanhante à autorização do médico plantonista ou utilizar frases como "essa lei não vale aqui". [...] Não dar informações claras sobre o estado de saúde da mulher, realizar procedimentos sem explicar ou ouvir sua opinião. [...] Não oferecer opções para alívio da dor. Impedir que a mulher se movimente, beba água ou coma alimentos leves durante o trabalho de parto. [...] Deixar a mulher sozinha, isolada ou trancada. [...] Realizar exames de toque vaginal repetidas vezes, sob o pretexto de "ensinar os estudantes a realizar o toque". [...] Fazer piadas, dar broncas, xingar ou impedir que a mulher se expresse durante o trabalho de parto. [...] Frases como: "Na hora de fazer tava bom, porque tá chorando agora?"; "Cale a boca, você quer que a criança nasça surda?"

De acordo com Chauí (1984, apud, TRAJANO; BARRETO, 2021), a partir do momento que o sujeito é considerado como “coisa”, é convertido a ser inerte e passivo. Nesse sentido, dizemos que há violência quando anulamos as ações e/ou as falas de outra pessoa. É importante reforçar que a violência não visa a destruição daquele que é considerado hierarquicamente inferior, mas sim a sua submissão.

A VO no Brasil atinge, sobretudo, os grupos de mulheres notoriamente excluídas. Isso indica que as desigualdades de gênero ainda existentes na sociedade brasileira impactam diretamente na maternidade/centro obstétrico e que, até hoje, o País tem dificuldades em dar respostas efetivas a esse problema por meio de Políticas Públicas. As evidências científicas apresentadas acima, mostram que a VO tem cor. Está presente na faixa etária de 20 a 34 anos. As mulheres têm baixa escolarização e são excluídas de informações sobre os procedimentos e sobre as decisões a serem tomadas sobre o seu corpo. A VO também tem endereço. Boa parte das mães são da região Norte e Nordeste e apresentam os mais vulneráveis indicadores sociais do Brasil (D’ORSI et al., 2014; LEAL et al., 2014; SOUZA, 2014; RODRIGUES et al., 2017; ZANARDO et al., 2017;

GUIMARÃES, JONAS & AMARAL, 2018; FIOCRUZ, 2019; SILVA et al., 2021; CESAR et al., 2022; SANTOS et al., 2022; SILVA et al., 2022).

Como estratégia de fortalecer melhorias nas condições do parto e nascimento, diminuição das cesáreas, menos intervenções no nascimento e diminuição da mortalidade materna e neonatal. O MS regulamentou a assistência das enfermeiras obstétricas brasileiras por meio da Portaria n. 2815/98 (BRASIL, 1998). Assim, o MS reconheceu a Enfermagem Obstétrica como campo de atuação profissional mais adequada dentro da proposta de humanização do processo de parto e nascimento e é a referência da equipe, favorável ao parto vaginal, influenciadora das boas práticas, principalmente no tocante à mitigar os indicadores e os índice de utilização e intervenções desnecessárias (BRASIL, 2011; LEMOS et al., 2022). Garante uma assistência que valoriza a mulher e suas singularidades (COFEN, 2016; SILVA et al., 2018) e atua contra a precarização da saúde pública e mantém com eficiência a oferta de serviços à população com equidade e qualidade (LIMA; SOUZA; SILVA, 2022).

A enfermagem obstétrica possui regulamentação para realização do pré-natal de baixo risco com 06 (seis) consultas com a gestante, durante as 40 semanas da gestação tanto em instituições públicas como em atendimento nas operadoras de saúde. A enfermagem desenvolve o papel de criar e fortalecer vínculo, esclarecer dúvidas, realizar instruções sobre a amamentação, direitos da mulher referente ao seu trabalho, sexualidade durante e após o parto, constrói o alicerce necessário para que essa mulher possa passar por todas as suas transformações físicas e emocionais. No entanto, quando a gestante entra no trabalho de parto e se dirige para as instituições de saúde, a peça principal não estará ao lado para concluir o seu trabalho que é o parto, no momento de maior fragilidade da mulher a profissional que a gestante confia não estará presente (BRASIL, 2012). Essa descontinuidade da assistência —, ausência de vínculo entre os serviços que realizam o pré-natal e a maternidade —, também foi apontada em outro resultado (GUIMARÃES; JONAS; AMARAL, 2018).

Para realização desse parto, a enfermagem obstetra está regulamentada pela Resolução COFEN 672/2021, bem como, deve ter na sua pós-graduação o mínimo de 600 horas na modalidade presencial (COFEN 2021; ALVES et al., 2015).

De modo que as características encontradas estão ligadas entre si e demandam um conjunto de estratégias articuladas com os vários segmentos governamentais e da sociedade civil. A análise possibilita compreender que o país não tem uma proposta de criação de uma política pública específica para tratar a VO; não existe um protocolo específico para atuar diante dos casos. Consequentemente, os profissionais de saúde, agentes públicos de proteção e garantia dos direitos não possuem legislação para fomentar a criação de projetos e planos de ações educativos para prevenir a VO. De modo que, a característica da VO Institucional é centralizadora e periférica (D'OLIVEIRA, DINI; SCHRAIBER, 2002; TRAJANO; BARRETO, 2021; LEITE et al., 2022).

A VO Institucional Centralizadora se materializa pela incapacidade técnica dos profissionais de saúde em atuar para empoderar as mulheres, pela ausência de proposta de intervenção diante dessa violência e pela negação do direito das mulheres pobres, de baixo poder aquisitivo, analfabetas e residentes em comunidades remotas serem mães.

Como também, a incapacidade dos profissionais de saúde, da gestão em compreender os impactos da banalização dessas condutas e da real situação das mulheres em situação de VO verbal, física, psicológica, sexual e institucional (CARVALHO; BRITO, 2018). Já na VO Institucional Periférica, o sistema de saúde age como agente de periferia, não oferecem equipes/equipamentos para oferecer insumos, segurança, respeito, alimentos, manter a mulher informada. Alguns profissionais de saúde não possuem condições de buscar alternativas assertivas de combate e prevenção a violência obstétrica (LEAL et al., 2017; ISMAEL et al., 2020). A análise evidencia a falta de conhecimento e o déficit da qualidade da consulta pré-natal (SILVA et al., 2021). Assim é necessário orientações para direcionarem seus trabalhos nessa questão apresentada (LEITE et al., 2022).

V. CONCLUSÃO

Os estudos analisados são de grande relevância para a ciência, além disso, orientam tomada de decisões, formação de políticas e garantia de direitos. Tal garantia, proporciona conforto e apoio emocional contínuo, como oferta de métodos não-farmacológicos de alívio da dor, facilita contato pele-a-pele, transmite segurança e auxilia na inibição de adoção de práticas não recomendadas e prejudiciais às mulheres e aos recém-nascidos (RN).

A Violência Obstétrica é resultante das desigualdades de gênero: têm sexo e idade (20 a 34 anos), tem cor/raça (negra, parda e indígena) tem classe social (pobre e classe média baixa), tem escolaridade (analfabetas, semi-analfabetas, e com baixa escolaridade). Tem endereço (residentes das regiões - norte e nordeste; habitantes de guetos e favelas); Apresenta características física, psicológica, sexual, moral e institucional.

VI. CONSIDERAÇÕES FINAIS

É importante a criação de grupos de estudos para realizar mapeamento da VO em todo território nacional e realizar reflexão crítica para formação de políticas exitosas com adoção de ferramentas tecnológicas para garantir humanização às mulheres. No sentido de construir conhecimentos baseados em evidências mais objetivo e aprofundando sobre o assunto. De modo a propor, estimular, promover e monitorar as políticas públicas de prevenção a VO.

É importante que a Rede de Proteção e Defesa (Delegacia, Instituto Médico Legal, Ministério Público e Poder Judiciário) e Apoio (Centro de Referência de Atendimento à Mulher, Casas-Abrigo, Casa da Mulher Brasileira, Coordenadorias de Violência contra a Mulher, Órgão da Defensoria Pública da Mulher) funcione interligada e articulada com a Clínica Ampliada, principalmente para proteger os agentes públicos que realizam a denúncia, para que seja garantido o sigilo da denúncia, quando necessário, desse profissional e para a vítima. Contudo, a atuação profissional desarticulada compromete o seu bom funcionamento.

É importante que o Ministério da Saúde construa um Caderno de Orientações Técnicas (COT) e com Plano de Prevenção, a ser implementado pelos profissionais de saúde e instituições, para que seja identificado os casos de ocorrência de uma VO, bem como, traçar os passos de como atuar e agir diante da ocorrência da VO e o legislativo propor a tipificação do crime de Violência Obstétrica.

É fundamental rever sobre a atuação da Enfermagem Obstetra, uma vez que, a mesma possui condições para atuar nas maternidades como plantonistas realizando os partos, mas esses profissionais que realizam os pré-natais, que atuam na Saúde Pública e Privada, estão impedidos de serem chamados para condução do parto dessas pacientes (SILVA et al., 2023)

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Clinical Appropriateness in the Suspicion of Venous Thrombosis of the Lower Limbs in the Emergency Department

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ABSTRACT

Background: Venous thrombosis of the lower limbs, with the thrombo-embolic complications that can derive from it, constitutes a potentially fatal disease, for which an ultrasound examination, which today represents the diagnostic method recognized as a gold-standard in venous pathology, performed the most rapidly possible is capable of reducing the morbidity and mortality associated with the acute thrombotic event, the incidence of relapses and distant sequelae.

Methods: The purpose of this study is to report and analyze the experience gained over ten years on patients sent to the emergency department of reference for the area with the presumed diagnosis of deep or superficial vein thrombosis of the lower limbs. From March 2001 to December 2011, 30350 patients were examined as an emergency; all underwent an accurate medical history, for the evaluation of the Wells score, and venous Doppler ultrasound examination of the lower limbs, with detailed CUS technique, only on the affected lower limb.

Keywords: venous thrombosis, venous ultrasonography, emergency department.

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ABSTRACT

Background: Venous thrombosis of the lower limbs, with the thrombo-embolic complications that can derive from it, constitutes a potentially fatal disease, for which an ultrasound examination, which today represents the diagnostic method recognized as a gold-standard in venous pathology, performed the most rapidly possible is capable of reducing the morbidity and mortality associated with the acute thrombotic event, the incidence of relapses and distant sequelae.

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Results: A positive diagnosis for acute phlebopathy in progress of patients undergoing urgent instrumental assessment, with detailed unilateral CUS technique, was detected in 7400 cases, which specifically concerned the deep tract more than the superficial one. The therapy was obviously diversified according to the pathology detected.

Conclusions: Based on the clinical experience conducted, it is clear that the thrombo-embolic pathology was found only in about a quarter of the cases sent to the specialist doctor, of which only a small number of patients needed hospitalization.

Keywords: venous thrombosis, venous ultrasonography, emergency department.

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I. INTRODUCTION

The significant and rapid development of non-invasive diagnostic equipment led to the design of the ecocolordoppler, a tool that has now taken a key role both in the diagnosis and follow-up of the venous "vascular patient". The validity of the ultrasonography (US) approach is well established in the diagnosis of thrombotic diseases, either deep or superficial, by several worldwide clinical trials. Indeed, only a few cases are left to contrast-based tests. Thus, the US test is the diagnostic method recognised by worldwide Guidelines as the gold-standard in venous diseases (Grade A), while venography should be considered only in a small number of patients with anatomical anomalies, malformations or when there is an indication for surgery on the deep venous system (Grade B) [1].

Deep vein thrombosis (DVT), and the thromboembolic complications that may ensue (pulmonary embolism, PE), is a potentially fatal disease, which often complicates the clinical

course of patients already suffering from other diseases, but is also able to affect apparently healthy individuals.

Healthcare providers and institutions must therefore be made aware of the need for citizens who develop symptoms consistent with DVT to be urgently referred to an appropriate diagnostic workup in order to ascertain the presence or absence of the disease. This is a prerequisite to make it possible to establish a timely and effective anticoagulant therapy capable of reducing the morbidity and mortality associated with acute thrombotic event, the incidence of relapses and remote sequelae.

For this reason the "Diagnosis of venous vascular urgency," service has been active for about ten years, with a specialist physician available every day from 8 am to 8 pm, at the Centre for Phlebolymphology of the University of Siena, whose task is to visit patients sent from the ER with a diagnosis of ongoing acute phlebopathy.

The purpose of this study is to report and analyze the experience gained over ten years with patients sent to the emergency room of the Santa Maria alle Scotte Hospital (Siena) with the presumed diagnosis of deep vein (DVT) or superficial (TVS) thrombosis of the lower limbs.

II. MATERIALS AND METHODS

Between March 2001 and December 2011, at the Centre for Phlebolymphology of the University of Siena, 3035 patients were considered with ecocolordoppler (ECD) (Siemens with 6.5-8.5 MHz linear probe), in the emergency room. 21160 were female (69.7%) and 9190 male (30.3%). The examined patients had come to the emergency room according to three referral modes: the urgent request of a general practitioner (45.2%), independently and later referred by the medical practitioner on duty in the emergency room (50.6%) or from a nearby centre not suited to carry out such an instrumental diagnosis (5.4%). All were administered a specific visit that included a thorough medical history to assess the Wells score, and ECD venous examination of the lower limbs by a medical specialist, with detailed technical CUS only focused on the lower limb involved.

The considered patient pool had a mean age of 65 years, ranging between 3 and 98 years, and if the seventh decade was the most representative for the female population, for the male it was the sixth. The requests sent to a trusted phlebology specialist turned out by 75,2% to be suspected DVT, 17.8% VBS and 7% other related diseases, with a slightly higher percentage in the right lower limb (52% right vs. 48% left). The ECD test was performed with the patient in the supine position for the investigation of the proximal femoral artery, and then in the prone position (with one leg above the other, alternately) for the popliteal portion and finally in a sitting position on the edge of the bed to examine the distal deep veins (stretching the veins promotes the display of anatomical detail). The posterior tibial compartment is visualised in the medial retromalleolar region, mostly in cross section, and the veins are displayed by squeezing the sole of the foot, while the anterior tibial veins are identified on the neck of the foot. You can directly and comprehensively examine the common femoral vein, deep femoral artery to the confluence with the common femoral vein, the superficial femoral artery, the popliteal artery, the sub-popliteal arteries at the convergence with the popliteal artery and, finally, the venous plexus of the calf. The exploration of the veins in the calf is quite time consuming, as it requires the examiner to have a special skill and to use suitable latest-generation equipment[2].

The presence or absence of DVT has been evaluated mainly with the compression test (compression ultrasonography = CUS), run by exercising adequate pressure with the probe on the venous tract to be examined. This allows you to determine if the walls of the vein fall into place or not, in fact, a fully compressible vein certainly does not contain any thrombi. It should be noted, however, that for various reasons some venous portions are difficult to compress (superficial femoral by Hunter's canal and deep femoral) and this can occur due to anatomical location, depth, overlap of bone and tendon structures, or, finally, for the presence of surrounding sclerotic tissue.

The compression test was performed both with a longitudinal and transverse scan. Its diagnostic accuracy is reduced at the distal end, where it has

sensitivity by 33%, specificity by 91% and a positive predictive value of 58%[3]. For all the examined patients Wells' score was used to calculate the level of clinical likelihood (pre -test) to suffer from an ongoing thrombotic process in place.

III. RESULTS

All patients were examined within a maximum of six hours from the arrival in the emergency room, with an average waiting time of about 2 hours. Surprisingly, this resulted in a final average value by -1.14 (low pre-test grade) while D-dimer dosage was not assayed for a statistically significant number of patients.

The diagnosis of patients undergoing urgent venous Doppler ultrasound of the lower limbs, using the described unilateral detailed CUS technique, was:

- In 64.4% of the sample, amounting to 19570 cases, no detectable pathology was in place;
- In 24.5% of the sample, or 7400 cases, an instrumental framework of acute phlebopathy was detected, involving the deep portion in 59.8% and the surface in 40.2%;
- In 11.1% of the sample, or 3380 cases, a correlated non-venous disease;

Going into more detail, taking into account only the 7400 acute phlebopathy cases, the thrombotic process was detected in different locations in the following percentages (considering only the most serious and the most proximal in the concomitant thrombosis):

- In 34.8% of 2580 cases, proximal DVT was detected (common femoral, superficial and deep);
- In 24.8% of the sample, 1840 cases, distal DVT was detected (Tab. I);
- In 40.2% of the sample, 2980 cases, SVT was detected (Tab. II).

As previously mentioned, an alternative diagnosis was achieved only in 11.1% (in the remaining percentage patients were referred to the emergency room without a definitive diagnosis) and, taking into account only related venous diseases, they were those described in Table III in order of frequency.

The therapy was obviously varied according to the disease: the 2580 proximal DVT were admitted to the Siena hospital in a medical ward, in order to administer the appropriate anticoagulant therapy.

Conversely, the 1840 distal cases were discharged with a therapeutic dose LMWH, compression bandaging and diagnostic check after three to five days. Instead, all the 2980 cases of SVT were discharged with LMWH at therapeutic dose and prescribed a 2nd class therapeutic elastic stocking compression (single stocking or knee-high depending on the extent of the thrombotic disease) and control after an average of about five to seven days.

IV. DISCUSSION

The clinical manifestations of DVT of the lower limbs are multiple (spontaneous pain or caused by the stretching of the muscles, redness, cyanosis, increased skin temperature, cramps, increase in the size of the limb, full fledged oedema, development of collateral circulation, phlegmasia alba dolens) however the clinical DVT diagnosis is not accurate because it is based on symptoms and signs (Bauer and Homans) which, individually or together, are not sufficiently sensitive and specific[4].

Precisely for this reason it is necessary to use a standardized diagnostic procedure to either confirm or rule out DVT, which must be administered rapidly, non-invasive, reproducible, sensitive and specific.

Ultrasonography with compression ECD (CUS) is one of three specific tests, together with clinical likelihood and D-dimer dosage, which constitute the diagnostic algorithm[5-6].

With regard to clinical likelihood, there are many factors associated with DVT, either predisposing or triggering, which affect onset, evolution and response to treatment, such as: history of previous DVT or pulmonary embolism episodes, recent surgery, immobilization, age, concomitant neoplastic disease, heart failure, trauma with tissue destruction, and/or fractures, oestrogen hormone therapy, pregnancy, obesity, genetically determined or acquired thrombophilia.

The existence of predisposing conditions or triggers should be considered in each individual patient, as they contribute in varying degrees to define the risk profile. This is clinically important to define, since performing the instrumental test to examine if the subject belongs to a high or low risk group affects the predictive value of the instrumental assessment from which the definitive diagnosis depends. The definition of risk is therefore critical to the decision-making process regarding the diagnostic process to be focused on each patient individually.

Different systems have been offered to quantify the clinical probability of DVT in individual patients. More specifically, in 1997 Wells developed a scoring system, which allows us to identify three categories of clinical probability: high, medium, low. This system combines medical records (neoplastic disease, immobilization of the lower limbs, bedding), data derived from physical examination of the patient (pain, swelling, venous collateralization), and an opinion as to the likelihood of an alternative diagnosis[7]. It all has been validated in a cross-sectional study based on systematic comparison with venography as the diagnostic standard of reference and in a longitudinal study based on the occurrence of clinical events, where it has been demonstrated that it can minimize the use of invasive procedures (venography) or non-invasive repeated (ultrasonography), without increasing the risk associated with false-negative diagnosis.

The ECD is a non-invasive method of choice for the diagnosis of proximal DVT of the lower limbs, as it has high diagnostic accuracy (sensitivity and specificity), ease of use, cost effectiveness and repeatability[8].

It allows the visualization of the venous system (venous wall and valves) and the representation of the real-time flow in various ways and in static conditions or during dynamic manoeuvres. The use of simple continuous wave Doppler device (CW Doppler) has been practically abandoned, because of its poor diagnostic accuracy[9]. The introduction of EDC has undoubtedly increased the possibility of recognizing and properly reviewing the venous structures at the distal level[10]. It should be pointed out, though, that especially for the examination of the distal veins, the ability of the operator and the use of suitable latest-generation equipment are key determinants in terms of the quality of the results of the US assay.

Additional diagnostic criteria are the absence of the Doppler and colour signal, spontaneous and/or caused, and direct visualization of the thrombus. Additional assays allow to assess the degree of echogenicity of the thrombus, its adhesion to the vessel wall (in particular, the presence of a floating proximal end) and its organization, although none of these issues has proven significant in the definition of the risk of pulmonary embolism[11-12].

Several scholars have offered the opportunity to examine not only the symptomatic limb, but also the contralateral one. As a matter of fact, a Canadian study performed on a large series showed that 80% of all DVT were unilateral and in the symptomatic limb, 15% were bilateral and only 5% were asymptomatic unilateral in the limb, but with thrombi limited to the sub-popliteal portion[13]. Therefore, it seems reasonable to conclude from these data that the presence of symptoms requires unilateral examinations, while a bilateral assessment seems appropriate only in patients with unilateral, though high-risk, symptoms or bilateral, as was the case in our diagnostic protocol.

The method is particularly accurate in the diagnosis of symptomatic proximal DVT and less satisfactory in the distal portion and asymptomatic patients in general. In the distal district it is possible to obtain substantial improvements with the growing experience and skill of the operators and the use of ecocolordoppler [3-10] that will produce, according to some authors, sensitivity values up to 100% and specificity by 79%, a positive predictive value (PPV) by 71% and negative predictive value (NPV) by 100%. It should be noted, however, that, to this day, we still lack a validation study concerning the proper exploration of the distal portion.

Recording a complete re-channelling or the persistence of a residual thrombus was crucial for

Recording a complete re-channelling or the persistence of a residual thrombus was crucial for a proper diagnosis in cases of suspected recurrence. Indeed, the detected compressibility of a previously free venous segment is a definitive diagnostic element, though it is not possible if there is no certainty about the previous framework to the onset of symptoms related to recurrent thrombosis. In addition, a significant change in the scale of a residual thrombus is a useful diagnostic element. The diagnosis of venous thrombosis in the superficial veins (SVT) is essentially clinical: inflammation, hardening, erythema, and tenderness along the course of the superficial veins makes it easy to tell this anatomical condition.

The US study (CUS) is especially suitable to evaluate the extent of the thrombotic process, which may not coincide with the extension of the inflammatory process[14], but especially to exclude its propagation to the deep veins of the system, which has been estimated to vary from 17 to 40%[15-16].

The most important clinical goals of timely and correct diagnosis and treatment of VTE focus on to reducing morbidity and mortality associated with its acute manifestations, reducing the incidence of further acute events, and finally contrasting the incidence of remote sequelae represented by the post-thrombotic syndrome, often highly debilitating and with high social costs (skin ulcers).

As reported in clinical trials worldwide, it is estimated that only around 30% of outpatient cases in which suspected DVT is actually confirmed by objective investigations. This data expresses the need to implement a proper diagnostic procedure to ensure an adequate and absolutely crucial – though not risk-free – treatment for those, and only those, who have an ongoing DVT. The awareness of this clinical issue is already widely spread, but the awareness of the importance of early diagnosis is much less widespread.

It has been calculated that, in the absence of anticoagulation, the risk of recurrent venous thrombo- embolism (VTE) is approximately 40% during the first month after the primary event and a further 10% in the second and third month[17], and every day spent without anticoagulation during the first month after the event is associated with a 1% absolute increase in the risk of relapse.[18]

Some authors have shown that the quality of heparin anticoagulation during the first days of therapy after diagnosis of DVT significantly influenced the incidence of thromboembolic recurrence in the long term, as insufficient heparin treatment in the first 24 hours associated with a greater frequency of relapses in the long run, even in the presence of a suitable oral anticoagulant therapy[19]. These results are in agreement with what was found in a randomised, where it has been shown that the absence of initial heparin treatment is associated with an unacceptably high frequency of relapses in the long - term[20-21].

The use of compression therapy in the course of DVT and for the prevention of SPT has become a well-established practice. Indeed, the usefulness of elastic compression, with anti-embolic stocking or permanent bandage in the initial phase and therapeutic elastic stocking (40 mmHg) for gait has been confirmed by observational studies. After 5 years of follow-up in patients with DVT, moderate post-thrombotic syndrome was observed in only 12% of the controlled population, while larger cases (ulcer or recurrent DVT) were detected only in 6% of the patients[22]. More recently it has been shown that the early application of elastic compression (within two-three weeks from the onset of the disease) reduces the incidence of post-thrombotic syndrome up to 57%[23], as later confirmed by a randomized trial in which therapeutic elastic stockings were used with high compression (30-40 mmHg) up to the highest point where the presence of a thrombotic process was detected[24].

Elastic compression maintains a crucial value even when the SPT was fully formed, thus reducing the severity and delaying its inevitable unfavourable development; indeed, recent evidence support higher incidence of thrombotic recurrence in those patients in whom the complete re-channelling of the veins affected by

the thrombotic process has not been obtained. To confirm this, the early application of elastic compression (2nd class therapeutic elastic stockings) since the DVT diagnosis, promotes faster and more complete re-channelling of the thrombus and therefore a lower risk of thrombotic recurrences and remote sequelae[25-26].

It is possible to conclude that in patients treated early with anticoagulant drugs and protected by therapeutic elastic stockings, the incidence of SPT is considerably lower than generally believed in the past, while there seems to be no correlation between the severity of the SPT and the extension of the initial thrombosis[27].

From the above it must be concluded that the timeliness and adequacy of heparin anticoagulation to be administered in the early days until valid anticoagulation with warfarin, is a key factor to reduce the recurrence of VTE not only during the first period after the acute event, but also after months, and also to reduce the severity of the post-thrombotic syndrome strongly influenced by the number of recurrences.

It is estimated that the percentage of cases in which a clinically suspected DVT is confirmed to be less than 50%[28-29-30-31-32]; this value is reduced to 30% if we limit ourselves to considering outpatient cases only[33-34-35-36-37].

Recently, a simplified mode of execution of the CUS has been offered, which provides only the examination of the common femoral vein in the groin and the popliteal vein at the popliteal fossa to its trifurcation, repeating the test after a week in the case of initial normality, or earlier in case of disorder worsening or the onset of new symptoms. The procedure has been validated in a prospective study including 1702 patients, with follow-up at 6 months, which showed a low overall incidence of thromboembolic complica tions (0.7%). The investigation thus conceived seems safe and effective, but requires to repeat the test in 70% of cases. However, it should also be noted that these results are attributable only to symptomatic outpatient cases, which prevent them from being adopted as standard protocol in our study.

Finally, a Doppler ultrasound study is warmly suggested by various clinical trails for a true evaluation of the extent of the thrombotic process in superficial phlebitis (especially in case of a thrombophlebitis of the great saphenous vein above the knee), in fact some authors consider it essential to repeat the test after a maximum of seven days for the possible proximal spread[38].

Even if such a theory does not yet exist a general consensus (this is an assessment that can also be entrusted only to the clinical inspection) in our study protocol was performed on all patients suffering from this disease[39].

V. CONCLUSIONS

Based on clinical experience applied to 30350 symptomatic patients in an outpatient setting, evaluated with unilateral CUS detailed EcoColorDoppler ultrasound method, we saw that the thromboembolic disease was found only in 24.5% of cases referred to a specialist, of which only 9.8% of patients required hospitalization for adequate oral anticoagulant therapy. Thus, from our prospective study, which last approximately 10 years, it appears that the request for an instrumental examination for suspected ongoing deep vein thrombosis of the lower limbs was definitely quite unnecessary (perhaps an excess of zeal for our patients or poor accuracy of the clinical signs) and should be rationalized in a better way. It is certain, though, that 4420 proximal and distal DVT detected in the first hours after the onset of appropriate therapy have benefited from the suitable therapy administered from the very beginning, thus presenting a significant reduction in morbidity and mortality associated with acute thrombotic event such as the incidence of periodic recurrences and/or the onset of venous skin ulcers and post-thrombotic aetiology, which in the literature represent about 60% of the total number of people affected by this condition[40-41].

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Table I: Distal DVTs

Popliteal vein	500	27.2%
Twin veins	770	41.8%
Solenoid veins	380	20.7%
Tibial veins	190	10.3%

Table II: Superficial Venous Thrombosis

Great Saphenous Vein	960	32.1%
Small Saphenous Vein	190	6.4%
Accesory Saphenous Vein	90	3.2%
Collateral vein	1740	58.3%

Table III: Non-Venous Clinical Pictures

Baker's cyst	1470	43.9%
Erysipelas/Lymphangitis	1000	29.8%
Hematoma	640	19.1%
Muscle tear/Lymphedema	240	7.2%

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Edie Russell, Bilal Javed , Yao Zhen & Furong Tian

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ABSTRACT

Menstruation is a natural occurrence for females of a fertile age and occurs for the potential possibility for pregnancy, menstruation can sometimes be an unpleasant experience for females. The aims of the present study were to investigate if the four nutraceutical active ingredients Pycnogenol, Lemon Balm, Ginger, and Saffron can individually decrease the severity of PMS, or decrease the severity of the symptoms related to PMS. The aim of this research was to concluded theoretically that the ingredients Pycnogenol, Lemon Balm, Ginger, and Saffron together as a supplement can treat menstrual related conditions, reducing the severity of the symptoms as a result of menstrual related conditions or disorders.

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Edie Russell[α], Bilal Javed[σ], Yao Zhen[ρ] & Furong Tian[Ꞥ]

ABSTRACT

Menstruation is a natural occurrence for females of a fertile age and occurs for the potential possibility for pregnancy, menstruation can sometimes be an unpleasant experience for females. The aims of the present study were to investigate if the four nutraceutical active ingredients Pycnogenol, Lemon Balm, Ginger, and Saffron can individually decrease the severity of PMS, or decrease the severity of the symptoms related to PMS. The aim of this research was to concluded theoretically that the ingredients Pycnogenol, Lemon Balm, Ginger, and Saffron together as a supplement can treat menstrual related conditions, reducing the severity of the symptoms as a result of menstrual related conditions or disorders.

PRISMA (Preferred Reporting Items for Systematic Reviews) was employed to study for four ingredient; Pycnogenol, Ginger, Lemon Balm, and Saffron on reducing PMS symptoms or reducing the severity of PMS. The search was focused on scientific research articles (Publication years between 1980 and 2022). 22 papers were selected in the analysis regarding the ingredient, concentration, number of people, year of publication, effect of symptom, references and Recommended Daily Allowance (RDA). The 32 current nutraceutical treatments products for PMS were gathered and evaluated.

23% of the sources used to show the effects of Lemon Balm on PMS symptoms, 36% of the sources used to show the effects of Pycnogenol on PMS symptoms. 18% of the gathered sources were saffron related, 23% of the sources are ginger related. Pycnogenol concentrations were ranging from 45mg-300mg across 7 different sources. Lemon Balm concentrations were ranging from 300mg-1200mg across 5 different sources. The rang of concentrations of Ginger were from 500mg-1500mg across 5 different sources. Saffron represented concentrations ranging from 30mg across 4 sources. The cost of estimated supplement was at rang of market price.

The current market of available in store PMS aid supplements in Ireland was analysed. This was done to evaluate the current nutraceutical treatments that are available for women in Ireland to help treat PMS/ help treat PMS symptoms instead of treating PMS with pharmaceutical medications like NSAID's. This showed there are very few supplements available in stores in Ireland that specifically aim to treat PMS or reduce PMS symptoms thus the development of the nutraceutical supplement with Pycnogenol, Lemon Balm, Ginger, and Saffron would be beneficial. The results of the marketing analysis showed there is no product containing just these four ingredients to treat PMS, thus providing a gap in the market for the development of this product.

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I. INTRODUCTION

Premenstrual syndrome is a set of moderate-to-severe physical and psychological symptoms that occur 1 to 2 weeks before having a period/menstruating and go away within the first

few days of menstruating. It is normal for a woman that menstruates to experience premenstrual symptoms such as stomach cramping, back pain, muscular pain, tender breasts, and bloating, but when these symptoms interfere with daily life it can be Premenstrual syndrome _(authors, 2021). PMS involves a range of physical, psychological and behavioural symptoms that recur during the luteal phase of the menstrual cycle and are relieved by the onset of menses or during the menstrual period. The most common symptoms of PMS are bloating, breast tenderness, fatigue, joint pain, irritability, and mood swings. Roughly 50-80% of women experience moderate to severe symptoms of PMS. Neurotransmitters and sex steroids are thought to play a role in the development and manifestation of symptoms of PMS (Veena Jasuja, 2014).

Symptoms of premenstrual syndrome can range from moderate to severe. These symptoms can include abdominal pain, back pain, low back pain, headache, swelling and tenderness in the breasts, nausea, anxiety, fatigue, mood swings and crying. The duration of these symptoms can vary from a few days to 2 weeks (Gudipally & Sharma, 2022). More than 150 physical and behavioural symptoms may be associated with PMS. The most common PMS symptoms are anxiety and mood swings (Watson, n.d.). These symptoms include digestive symptoms such as bloating, nausea, constipation, diarrhoea, vomiting, and increased appetite. Some emotional and mood symptoms may include mood swings, anxiety, depression, confusion, poor concentration, and irritation (Watson, n.d.).

More specifically Premenstrual syndrome (PMS) is characterised by a collection of recurrent moderate-to-severe physical, behavioural, and somatic symptoms that develop during the luteal phase of the menstrual cycle, occurring 7-10 days prior to the beginning of menstruation and are usually relieved at, or shortly after commencement of menstrual flow (Aeli Ryu, 2015).

Typically PMS involves at least a few different symptoms rather than only one symptom. These symptoms can vary from person to person, and the severity of these symptoms can also vary from person to person. PMS symptoms can be severe enough to affect a woman's regular routine (The Healthline Medical Network, 2020).

There are many symptoms as a result of premenstrual syndrome. The symptoms of PMS can include mood swings, tender breasts, depression, anxiety, bloating, headaches, stomach pain, stomach cramps (painful muscular cramps in the tummy), muscular pain, back pain, sleep disturbances, constipation, and diarrhoea (David R. Rubinow, 1997). The most common symptoms of PMS include back pain, mood swings, anxiety, depressive episodes, stomach cramps/stomach pain, muscular pain, nausea, and headaches (NHS, 2021).

Depression and anxiety disorder are similar to PMS, the difference is that the symptoms of PMS occur only in the days preceding to the beginning of menstruation (Robert F Casper, 2021).

It is estimated that as many as 3 of every 4 menstruating women have experienced premenstrual syndrome (staff, 2022). The causes and aetiology of PMS has not been clearly defined, and scientific research has not led to a conclusive cause of PMS or an explanation for why some women experience PMS more severely than others (The Healthline Medical Network, 2020)

There is currently no sure and no specific treatment for PMS, no single treatment works for everyone. No single test can diagnose PMS (staff, 2021). To be diagnosed with PMS, a woman must have physical symptoms such as breast tenderness and bloating as well as mood changes such as depressive episodes. These symptoms must occur before a menstrual period and disappear after the onset of the period (Robert F Casper, 2021) .

1.1 Pycnogenol

Maritime Pine trees (Pinus Pinaster) grow in countries on the Mediterranean Sea, Maritime pine trees that grow in southwest France are used to make Pycnogenol, the trademark name for a specific maritime pine bark extract (Web MD, n.d.).

Pycnogenol (maritime bark), like willow bark is a nutraceutical material that has been used since

ancient times (used for more than 2000 years). Pycnogenol has been considered helpful for wound healing, treating scurvy, healing ulcers, and reducing vascular inflammation. Pycnogenol contains active polyphenols including catechin, taxifolin, procyanidins, and phenolic acids (Kyung-JooChoa, 2000) (Joseph C. Maroon, 2010).

Studies have also shown that Pycnogenol is 50-100 times more potent than vitamin E in neutralizing free radicals, prolonging the activity of vitamin C and E (Joseph C. Maroon, 2010).

Pycnogenol contains a mixture of phenols (organic compound with hydroxyl group (-OH) attached to a carbon atom in a benzene ring) and polyphenols (multiples of phenol units) such as the flavonoids catechin, epicatechin, taxifolin and condensed flavonoids, including procyanidin B1, B3, B7, and others. Pycnogenol also contains phenolic acids such as caffeic acid, ferulic acid, and p-hydroxybenzoic acid (L Packer, 1999).

1.2 Saffron

Saffron is derived from Crocus Sativus flower. The dried stigmas of the flower (thread-like parts) are used to make saffron spice (WedMD, n.d.).

Saffron the spice is derived from the flower of Crocus Sativus also known as Saffron Crocus. It is believed that saffron originated in Iran. Greece and Mesopotamia have also been suggested as the potential region of origin of this plant (Anon., 2022).

In terms of Phytochemicals, Saffron is rich in carotenoids and terpenes. The two main products of saffron are carotenoids deriving from zeaxanthin, pirocrocin and safranal. Saffron and its compounds have antioxidant and anti-inflammatory properties in vitro and in vivo (Adil El Midaoui, 2022).

Studies have examined the effects of saffron on neuropsychiatric diseases, these studies have suggested that saffron constitutes an effective treatment for depression, anxiety, and schizophrenia (Adil El Midaoui, 2022). According to a recent study "the clarification of the molecular mechanisms by which saffron and its compounds exert their beneficial effects will make it possible to optimize their effectiveness and rationalize their use for the benefit of human health" (Adil El Midaoui, 2022)

1.3 Ginger

Ginger root (underground stem) is the rhizome of Zingiber Officinale plant, a herbaceous perennial plant of the ginger family/Zingiberaceae family (Mahr, n.d.).

Ginger originated in Maritime Southeast Asia, it was then transported throughout the Indo-Pacific. Ginger is one of the first spices to have been exported from Asia, arriving in Europe with the spice trade, and was used by Ancient Greeks and Romans (Anon., 2022).

Ginger which belongs to the Zingiberaceae family as previously mentioned has been commonly consumed as a spice and herbal medicine for a long time. Ginger root has been used to attenuate and treat several common diseases, such as colds, headaches, nausea, and emesis (Qian-Qian Mao, 2019).

There have been many bioactive compounds identified in ginger, such as phenolic and terpene compounds. The phenolic compounds in ginger are mainly gingerols, shogaols, and paradols. There are also other phenolic compounds in ginger, such as zingerone, quercetin, and 6-dehydrogingerdione. Ginger possesses multiple bioactivities such as antioxidant, anti-inflammatory, and antimicrobial properties.

Ginger has been traditionally used to treat gastrointestinal symptoms, recent research has showed ginger to be effective supplement to alleviate nausea (Qian-Qian Mao, 2019).

Ginger has been used in Chinese and Indian medicine for thousands of years. Ginger may help relieve nausea, and aid digestion. The antioxidants and other nutrients in ginger may help prevent or treat inflammation and various types of infection (Fletcher, 2022).

1.4 Lemon Balm

Lemon Balm also known as Melissa Officinalis is a perennial herbaceous plant from the mint family,

native to south-central Europe, the Mediterranean Basin, Iran, and Central Asia. Lemon Balm has been traditionally used to improve mood and relieve symptoms of stress. (Anon., 2022).

Lemon Balm (Melissa Officinalis) is a herb from the mint family, the leaves which have a lemon aroma are used to make medicine and flavour foods. People use lemon balm for stress, anxiety, indigestion, insomnia and many other condition, although there is a lack of clarification in identifying the molecular mechanisms by which lemon balm exerts its beneficial effects (WebMD, n.d.).

In terms of Phytochemicals, Melissa Officinalis is a plant rich in biologically active compounds which is used worldwide for its therapeutic effects. Studies on its composition have shown that it contains mainly flavonoids, terpenoids, phenolic acids, and tannins. The main active constituents of Lemon balm are volatile compounds such as citronellal and geraniol, triterpenes including oleanolic and Ursolic acid, phenolic acids including caffeic acid and rosmarinic acid, and flavonoids such as quercetin and luteolin (Gabriela Petrisor, 2022).

These components may be responsible for several effects seen in vitro, including antioxidant properties and an affinity for binding to both nicotinic and muscarinic receptors in human brain cortex tissue. In terms of the potential mechanism in which lemon balm works, the end of this mechanism is of interest in relation to melissa officinalis, as modulation of the cholinergic system can be beneficial to cognitive function. Although the mechanism by which melissa increases ratings of calmness, reduced alertness, and improved performance is still unknown. Cholinergic nicotinic respond to acetylcholine which is released by nerve cells in the brain when people are under stress (Marcin Ozarowski, 2016).

1.5 Current PMS Treatments

The standard current treatments recommended in Ireland by doctors and pharmacists include; antidepressants (specifically selective serotonin reuptake inhibitors (SSRIs)) to treat low mood including depressive episodes and mood fluctuations/mood swings (usually as a result of fluctuations of the levels of hormones during the menstrual cycle), Non-steroidal anti-inflammatory drugs (NSAIDs) and various pain killers to treat cramping and breast discomfort, diuretics for fluid retention, hormonal contraceptives to theoretically prevent the occurrence of ovulation which prevents ovulation related hormone changes, and diet altercations such as salt restriction to avoid fluid retention (Magovern, n.d.). The figure 1 summarised the symptoms occur on the body and which ingredients in the product treat.

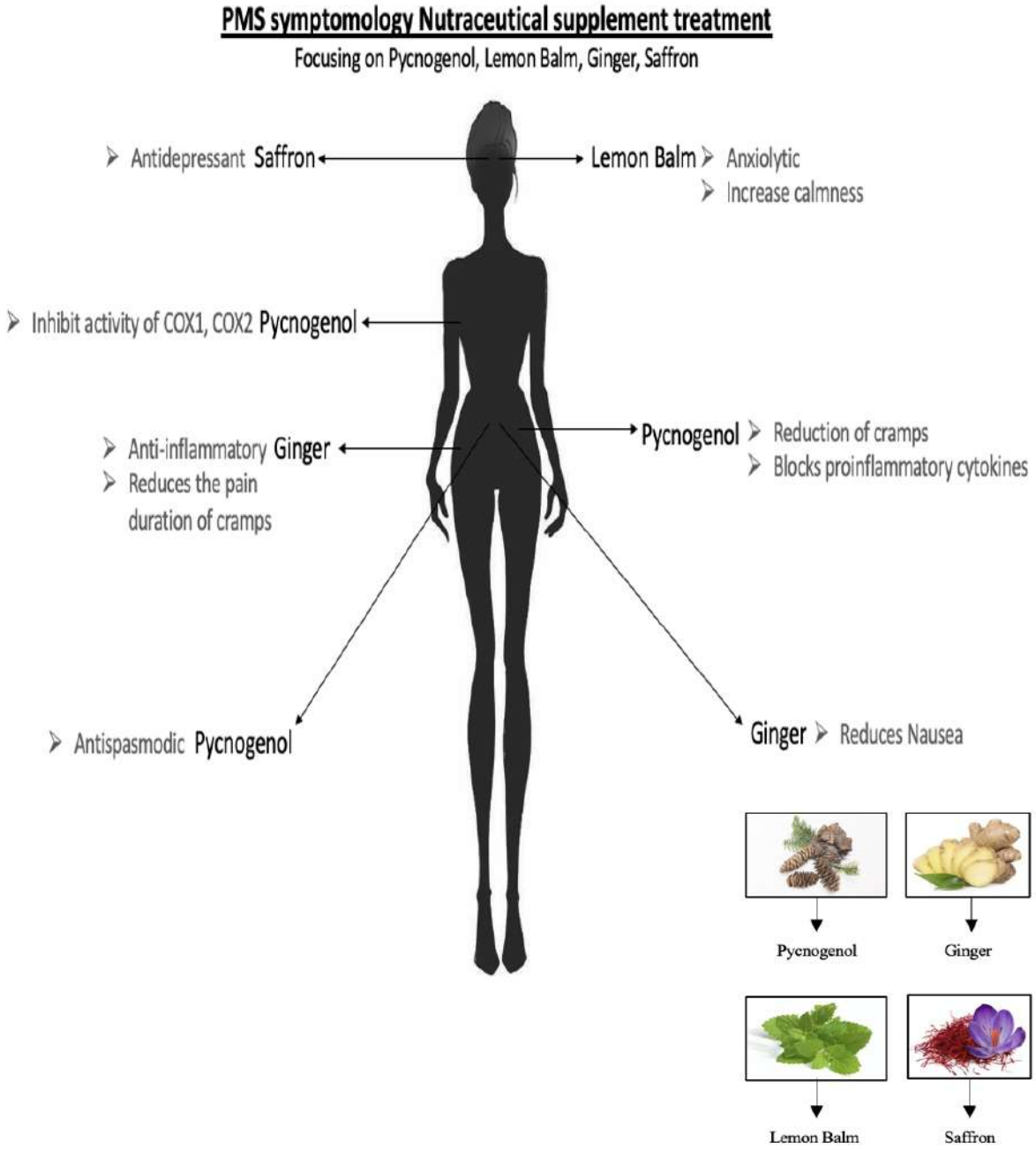

Figure 1: Symptomology of PMS, a Diagram of Where the Symptoms Occur on the Body and Which Ingredients in the Product Treat Which Symptom

Statistics

Table 1: The Percentage of Women Affected by PMS per Source

	Percentage affected	Source
1.	75% of Menstruating women experience PMS	(Belluz, 2015)
2.	90% of women of reproductive age experience PMS symptoms	(Petranka Chumpalova, 2020)
3.	59% Irish women's daily lives are affected by PMS	(Mcknight, n.d.)
4.	90% of women suffer from some form of PMS	(Health, n.d.)
5.	85% of women of childbearing age suffer from at least one symptom of PMS	(REYNOLDS, 2017)
6.	80% of women experience PMS	(Kulkarni, 2018)
7.	92.3% of students experience PMS	(Jumana Hussein Shehadeh RN, 2017)

The purpose of this review is to research and evaluate the effectiveness each nutraceutical ingredient has on treating PMS or reducing symptoms related to PMS individually. As such high levels of women suffer with PMS, the development of a nutraceutical supplement would be beneficial to those suffering, as well as giving women the option to naturally treat PMS rather than using pharmaceuticals. Combining the gathered research and evaluating whether the ingredients together Pycnogenol, ginger, lemon balm, and saffron can developed into a PMS aid supplement.

II. METHODS

2.1 PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)

A PRISMA 2020 checklist was finished and a flowchart was constructed following the PRISMA guidelines and registration information. The selection process was based on the PRISMA statement 2020 _(Matthew J Page, 2021), the

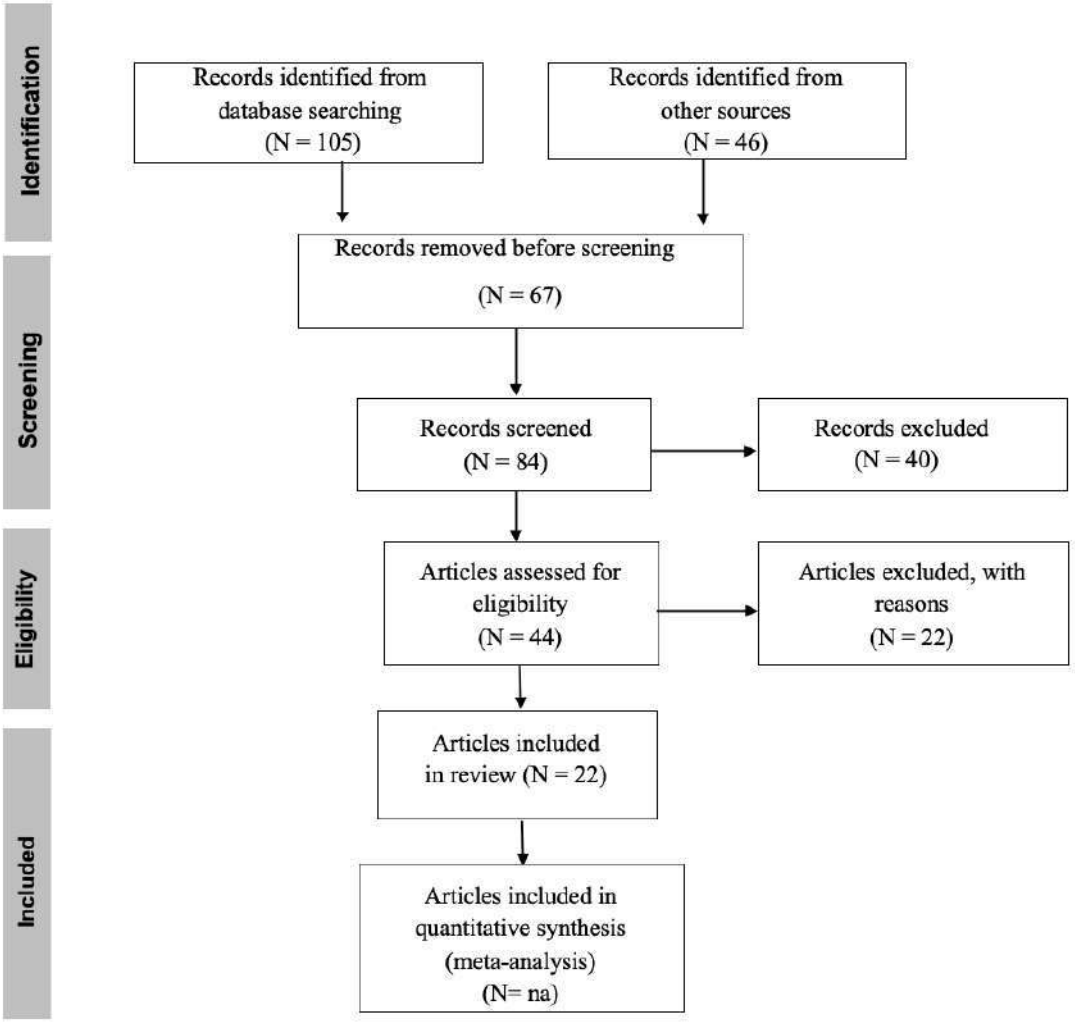

Figure 2: PRISMA Flow Diagram for Literature Search; Na = Not Applicable

2.2 Research Process

Focusing on the effects each nutraceutical active ingredient; Pycnogenol, Ginger, Lemon Balm, and Saffron has on reducing PMS symptoms or reducing the severity of PMS. The systematic review was gathered through a literature search from online databases. Relevant articles were searched on Google scholar, PubMed, and Scopus database to identify the Aetiology of PMS and the positive effects in reducing PMS symptoms/PMS severity when individually consuming each nutraceutical active ingredient separately (Pycnogenol, Lemon Balm, Saffron, Ginger).

Boolean operators "AND" and "OR" were used to broaden the search. Some different key words used for searching were "PMS", "Pycnogenol", "Lemon Balm", "Ginger", "Saffron", "natural anti-inflammatory", "natural hormonal adaptogen", "anxiolytic", and "natural GABA booster". The key words used for searching was "PMS" or "Premenstrual syndrome". The articles were identified through the Scopus database, Google Scholar, and PubMed online. The citations were collected from articles and different studies withing the last 30 years.

The Search Focused on Scientific Research Articles Using the Following Protocol-

1. Publication years between 1980 and 2022
2. The keywords "PMS" or "Premenstrual syndrome" had to appear in the title and abstract.
3. They had to be scientific indexed papers only.

The results were screened against inclusion criteria, for example; articles that were not relevant to the studies. The full text of papers for all the articles that fit into the inclusion criteria was retrieved.

2.3 Screening

Strict criteria was used to determine the relevant articles for inclusion. For example, articles were excluded if published in languages other than English, or for which only an abstract was available, and then each remaining search result was grouped as one of the articles.

1. "Primary articles" research papers appeared in the peer-reviewed literature and reported original data or results based on observations and experiments.
2. "Review" papers summarized the understanding of PMS and the effect of each nutraceutical active ingredient separately on reducing the severity of PMS or PMS symptoms.

Throughout the screening process, the number of publications excluded in each stage and their reasons for exclusions were noted based on the guidelines outlines in the PRISMA statement 2020 in Figure 2.

2.4 Researching Nutraceutical Active Ingredients to Treat PMS Severity and PMS Symptoms

The aetiology of PMS, hormones involved, symptomology, and the different pathways of current PMS treatments that specifically reduced the severity of PMS or reduced PMS symptom severity was investigated to further research potential nutraceutical supplement treatment options with more understanding. This was done by reading scientific articles, online articles, books, and listening to podcasts. Research articles, scientific articles, and scientific experiments were searched online. This was done using google and the TU Dublin library resources by using different key words, "PMS", "Premenstrual Syndrome", "pathophysiology", "aetiology", "symptomology", "PMS treatments" and "PMS symptomology pathways". Each article found with relevant information was read. Common symptoms were identified and reasons for affective PMS treatments were identified.

Once the most common symptoms were identified, common nutraceutical active ingredients that claim to help reduce an individual symptom of PMS were researched. Scientific articles and scientific experiments focusing on different nutraceutical or common nutraceutical active ingredients used to specifically treat PMS, reduce PMS severity, and reduce symptoms related to PMS were researched. After understanding and researching symptomology of PMS, and researching the potential pathways targeted for treatment. For example the arachidonic acid pathway is a component of the inflammatory pathway, arachidonic acid is released from traumatized cellular membranes. The expansion of knowledge on the inflammation pathways was beneficial in researching ways to prevent or inhibit inflammation through interrupting inflammatory pathways. Four nutraceutical active ingredients were chosen with the most evidence and most research supporting the positive effects of the ingredient in reducing PMS severity, or reducing PMS symptom severity.

As Anxiety was a very common symptom of PMS, anxiolytic supplements were researched. Lemon Balm was one of the common supplements used

to treat anxiety and PMS related anxiety. There was a large amount of research done on Lemon Balm, and there were several experiments with positive results in reducing PMS related anxiety.

Further research was done online on Lemon Balm and PMS, therefore lemon balm was chosen as one of the nutraceutical active ingredients included in the research of a PMS aid supplement.

Research has claimed the mechanisms of action of white willow bark is very similar to aspirin. White willow bark is an old herbal remedy for pain and inflammation, used as an analgesic and antipyretic agent (Joseph C. Maroon, 2010).

Further research was done on natural anti-inflammatories as the symptoms of PMS include cramping, back pain, and pain due to inflammation. During the investigation of white willow bark, Pycnogenol was identified as another natural anti-inflammatory. Further research was done on Pycnogenol online on treating symptomology of PMS and reducing PMS severity. As several experiments were found, Pycnogenol was chosen as the second nutraceutical active ingredient included in the research of a PMS aid supplement.

As mood swings and depressive episodes are symptoms of PMS, a natural anti-depressant supplement was researched. There were several experiments done on the positive effects of consuming saffron for depression and low moods. Saffron was the third nutraceutical active ingredient chosen to be include in the research of developing a new PMS aid supplement.

As back pain, cramping, abdominal pain, nausea, and headaches are common symptoms of PMS. Natural anti-inflammatory nutraceutical supplements, and anti-nausea nutraceutical supplements were researched. Ginger was a common supplement in treating PMS related nausea as well as being a common supplement for treating PMS related inflammation and pain. The fourth nutraceutical active ingredient chosen was ginger for treating both symptom nausea and pain as articles and experiments were found on ginger reducing PMS symptom severity of nausea and pain.

For each chosen ingredient, scientific articles and experiments were researched, the relevant results and data from each experiment and article were noted along with the reference to the source. The effectiveness of Ginger reducing PMS symptoms was searched, the relative articles and experiments were read and the findings from each article or experiment was noted. This was done for each ingredient.

III. RESULT

The table 2 below displays the results of the methods 2.1, 2.2, 2.3, 2.4. The results of the research process after the screening process was applied. The table includes information gathered from relevant articles in relation to Pycnogenol, Lemon Balm, Ginger, and Saffron effectively reducing PMS related symptoms, reducing PMS severity or treating PMS, effectively alleviating symptoms related to menstrual disorders and the symptoms as a result of fluctuations of hormonal levels throughout the menstrual cycle. There were 22 papers in table 2. The order of column from left to right were ingredient, concentration, number of people, year of publication, effect of symptom, references and Recommended Daily Allowance (RDA).

Table 2: Experimental Research findings

Ingredients	Concentration		No. of people	Year	Effects	Reference
Pycnogenol	1	100-200mg	*Systemic review*	2010	Pycnogenol inhibits TNF-a induced NF-kB activation, therefore inflammatory response is decreased.	(Joseph C. Maroon, 2010)
	2	200mg	7	2006	Pycnogenol has anti-inflammatory effects through the reduction of MMP-9 and inhibition of NF-kB activation.	(Tanja Grimm, 2006)
	3	60mg	116	2008	Lowered pain during menstruation, seen by a significant reduction of NSAID usage, the number of days due to Dysmenorrhea, which decreased from an average of 2.1 days prior treatment to 1.3 days after treatment.	(Nobutaka Suzuki, 2008)
	4	30-60mg	39	2002	Reduce symptoms in 70% of the females in an open clinical study, these females either had endometriosis and/or menstrual pain.	(rohdewald, 2002)
	5	60mg	42	2004	Reduced the intake of analgesics, the number of days with pain and reduced the intensity of low back pain, and abdominal pain in 42 women suffering PMS related pain symptoms. could be used as an alternative to Gn-Rha for the treatment of endometriosis	(Kohama T, 2004)
	6	200mg	66	2006	73% decrease in cramp attack episodes over 4 weeks. Cramp attacks decreased from 8.6 to 2.4 cramp episodes a week.	(G. Vinciguerra, 2006)
	7	300mg	10	2005	a statistically significant reduction in COX enzyme activity due to 300mg of Pycnogenol taken, relieving symptoms of inflammation and pain.	(Angelika Schäfera, 2005)
	8	60mg	58	2007	Over 48 weeks the results of supplementation showed reduction in pelvic pain, abdominal pain due to PMS and did not disrupt the cycle	(Anon., 2007)
Lemon Balm	1	1200mg	100	2014	Reduced psychological, social, and physical symptoms off PMS after treating women with PMS for 3 cycles	(Marzieh Akbarzadeh, 2014)
	2	300mg	50	2014	Pain reduced on a scale of 1-10 from 6.30 to 3.94 and 3.24. the pain duration before treatment was 1-6 hours, after the treatment the pain duration was reduced to less than one hour.	(Ramezan Kalvandi, 2014)

	3	330mg	90	2018	Lemon balm did not increase the severity of bleeding and the duration of menstruation. Lemon balm reduced the severity of all systemic symptoms, and reduced the neurological symptoms fatigue, and lethargy.	(Parvaneh Mirabi, 2018)
	4	1000mg	93	2016	Lemon Balm reduced the severity of PMS symptoms, increasing the quality of life of the women with PMS significantly. 93.5% students treated with lemon balm were satisfied with their treatment (29 out of 31 students).	(Mojgan Mirghafourvand, 2016)
	5	600mg	18	2004	Lemon Balm significantly increased self-ratings of calmness and reduced self-ratings of alertness in relation to PMS symptoms of decreased calmness	(David O Kennedy, 2004)
Ginger	1	500mg	70	2014	ginger significantly reduced the total score of PMS in terms of severity of mood, and physical and behavioural symptoms of the first month intervention.	(Samira Khayat, 2014)
	2	1500mg	105	2012	Eleven hour less pain duration in physical symptoms associated with dysmenorrhea and PMS by ginger. Relieved pain in women with primary dysmenorrhea administered at the onset or during the 3 days prior to menstruation.	(Parvin Rahnama, 2012)
	3	1000mg	150	2007	In comparing the use of ibuprofen to treat pain related to dysmenorrhea, ginger was as effective in relieving pain from dysmenorrhea	(Giti Ozgoli, 2007)
	4	500mg	Systemic review	2016	Systemic review suggesting Ginger to be an natural anti- inflammatory for pain related to PMS.	(Birgit M. Dietz, 2016)
	5	750-2000mg	Systemic review	2015	29 articles suggested effectiveness of ginger to treat dysmenorrhea and PMS, in reducing the severity of symptoms.	(James W Daily, 2015)
Saffron	1	30mg	40	2005	Saffron at the dose of 30ng a day in comparison to fluoxetine 20mg a day for the treatment of mild to moderate depression was just as effective and similar to fluoxetine the antidepressant, saffron would be justified to be used in treating mild to moderate depression.	(A A Noorbala, 2005)
	2	30mg	50	2008	50% decrease in the severity of PMS in 75% of the women. Saffron through serotonergic mechanism shows an antidepressant effect in the treatment of women with mild to moderate depression, and	(M Agha-Hosseini, 2008)

					dysregulation of the serotonergic system can be a potential mechanism for the majority of PMS symptoms	
	3	30mg	78	2016	76% of women that experience PMS symptoms reported a 50% reduction in the severity of PMS symptoms. A 50% alleviation of depression symptoms in 60% of women reported.	(Soheila Pirdadeh Beiranvand, 2016)
	4	Saffron odour for 20 minutes	35	2011	Results indicate that Saffron odour exert some effects in treatment of PMS, dysmenorrhea and irregular menstruation as well as menstrual distress.	(Hajime Fukuia, 2011)

The information gathered from each article involved noting the amount of people involved in the article or experiment, the concentration of the nutraceutical active ingredient used in the experiment or article, the year the article or experiment was from, and the beneficial effects of the nutraceutical ingredient. The first source of information in relation to Pycnogenol and alleviating PMS symptoms involved a systematic review with concentrations ranging from 100-200mg, this review took place in 2010. The beneficial effects of this systematic review on Pycnogenol reducing PMS symptoms was noted in table 2, the reference for this information was also displayed. On the right hand side the Recommended daily allowance or the Safe amount of Pycnogenol, Lemon balm, Ginger, and saffron is also displayed in the final column.

The concentrations in each study per ingredient were tabulated and were displayed in figure 3. The figures with the heading concentrations refers to the concentrations of the nutraceutical active ingredient used in the experiment or article, In 3 the concentrations used per study per ingredients is represented by a histogram.

3.2 Concentrations Per Ingredient used Per Study

The concentrations used in the 22 articles and experiments involved in the results of this study are represented by the histogram below in figure 3.

Shown in figure 4, a pie chart representing the percentage and fraction of articles gathered per ingredient. For example 8 articles/experiments were gathered and used in the results for discussion about Pycnogenol which is represented by the green segment of the pie chart.

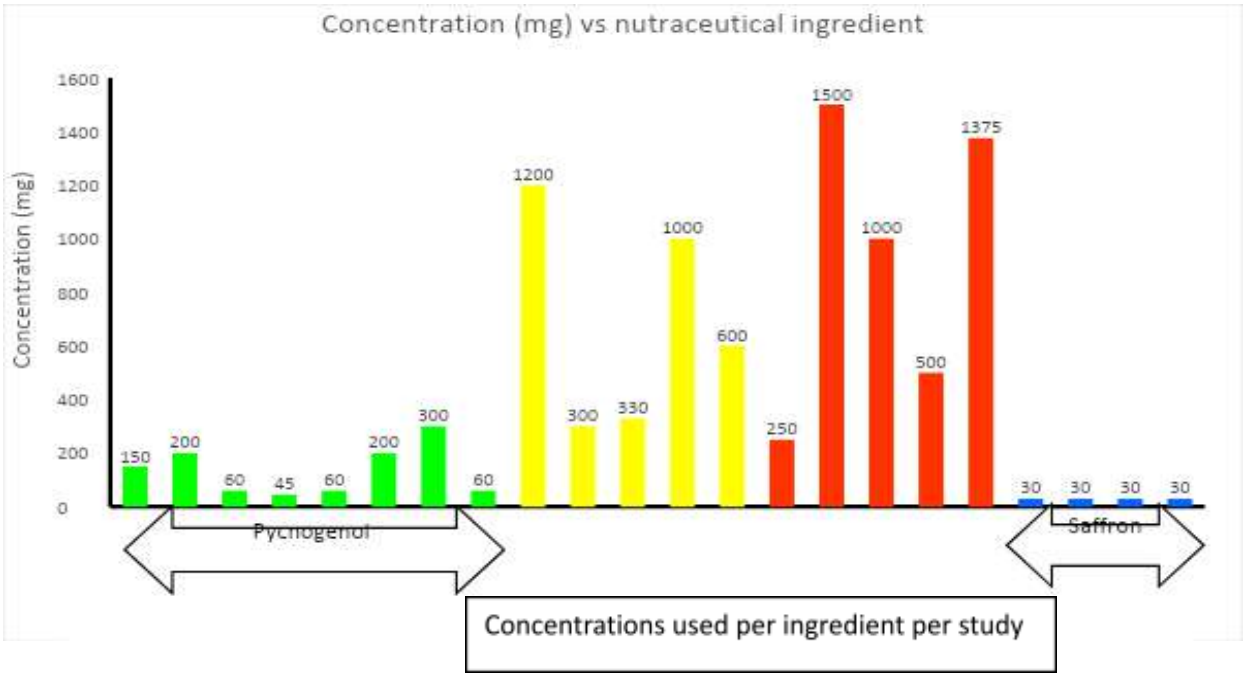

Figure 3: The Concentrations in Mg per Ingredient Used in Each Study, the Lemon Balm in Yellow, Pycnogenol in Green, Saffron in Blue, Ginger in Red

Pycnogenol represented by the green bars, concentrations used in the studied included were ranging from 45mg-300mg across 7 different sources. Lemon Balm represented by yellow bars, concentrations ranging from 300mg-1200mg across 5 different sources. Ginger represented by red bars, concentrations ranging from 500mg-1500mg across 5 different sources.. Saffron represented by the blue bars, concentrations ranging from 30mg across 4 sources.

The figures with the heading concentrations refers to the concentrations of the nutraceutical active ingredient used in the experiment or article, In figure 3 the concentrations used per study per ingredients is represented by a histogram. The histogram shows the milligrams of each nutraceutical active ingredient used per study that proved to be effective in relation to treating PMS and PMS related symptoms and or menstrual related symptoms, including the treatment of endometriosis, PMDD, PMS and other menstrual disorders. The calculations below represent the average concentration used per ingredient.

1. Pycnogenol Concentrations (represented by the green bars):
2. Average concentration of Pycnogenol used was 134mg.
3. Lemon Balm concentrations (represented by the yellow bars):
4. Average concentration of Lemon Balm used was 586 mg.
5. Ginger concentrations (represented by the red bars):
6. Average concentration of Ginger used was 925mg
7. Saffron concentrations (represented by the blue bars):

Average concentration of Saffron used was 30mg

3.3 Statistics of the research articles

Twenty two articles were included in the results, as shown in table 2 eight of these articles were about Pycnogenol and treating PMS, five of these articles were about Lemon Balm treating PMS, five of these articles were about Ginger treating PMS, and four of these articles were about Saffron treating PMS. Figure 4 represents the fraction of articles representing Pycnogenol, Lemon Balm, Ginger, Saffron.

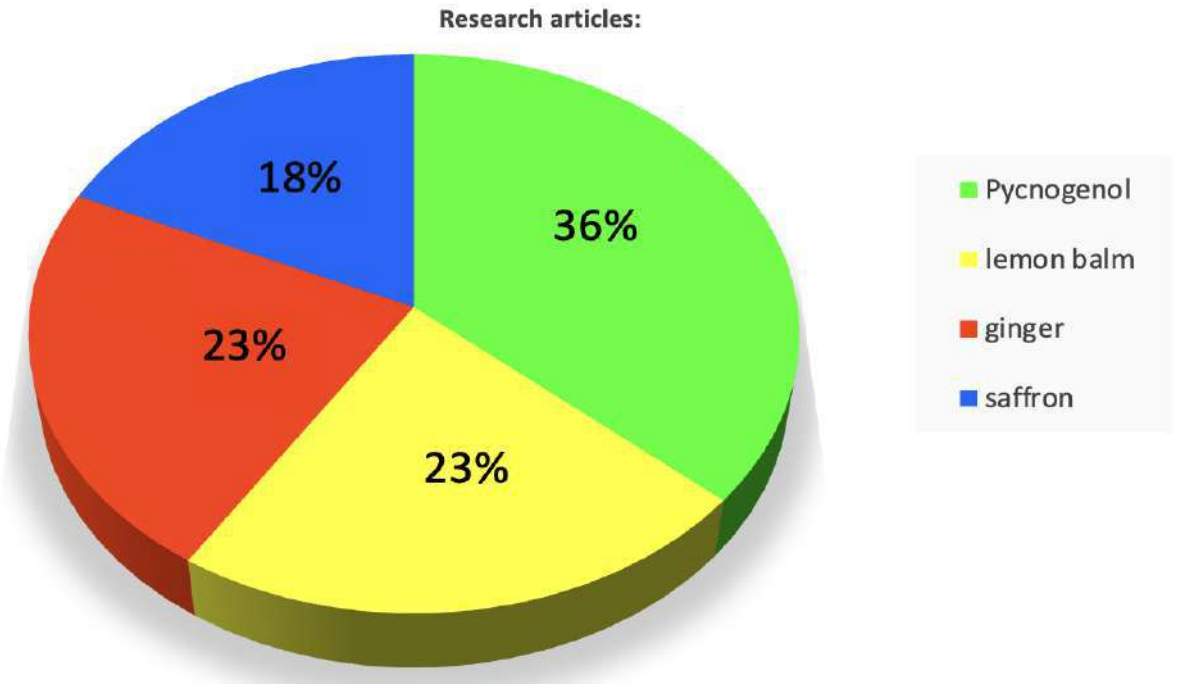

Figure 4: Pie Chart with Percentages Representing the Number of Research Articles used per Ingredient. the Lemon Balm in Yellow, Pycnogenol in Green, Saffron in Blue, Ginger in Red

Yellow segment representing lemon balm, 23% of the sources used to show the effects of Lemon Balm on PMS symptoms. Pycnogenol represented by the green segment is 36% of the sources used to show the effects of Pycnogenol on PMS symptoms. The blue segment represents Saffron, 18% of the gathered sources were saffron related. The red segment represents the articles gathered about ginger, 23% of the sources are ginger related.

Referencing back to figure 3, which showed the range of concentrations used per article/ ingredient per ingredient, figure 4 shows the theoretical concentration that would be used in the PMS supplement based off the average calculations of the concentrations done previously as well as taking the concentration that was most frequently used into account.

3.4 Concentration of Each Active Ingredient in the Theoretical New Product to Treat PMS in Comparison to the Recommended Daily Allowance

The theoretical concentrations of each nutraceutical active ingredient that was in the supplement to treat PMS was estimated and compared to the recommended concentrations that would be safe to ingest and would not cause harm to the consumer. As mentioned in table 2, the safe concentrations recommended in the last column of the right hand side, these numbers were used in this histogram for comparison of the theoretical product below in figure 5. The theoretical concentrations that were used in the PMS supplement were calculated using the most frequently used concentrations from the literature reviews.

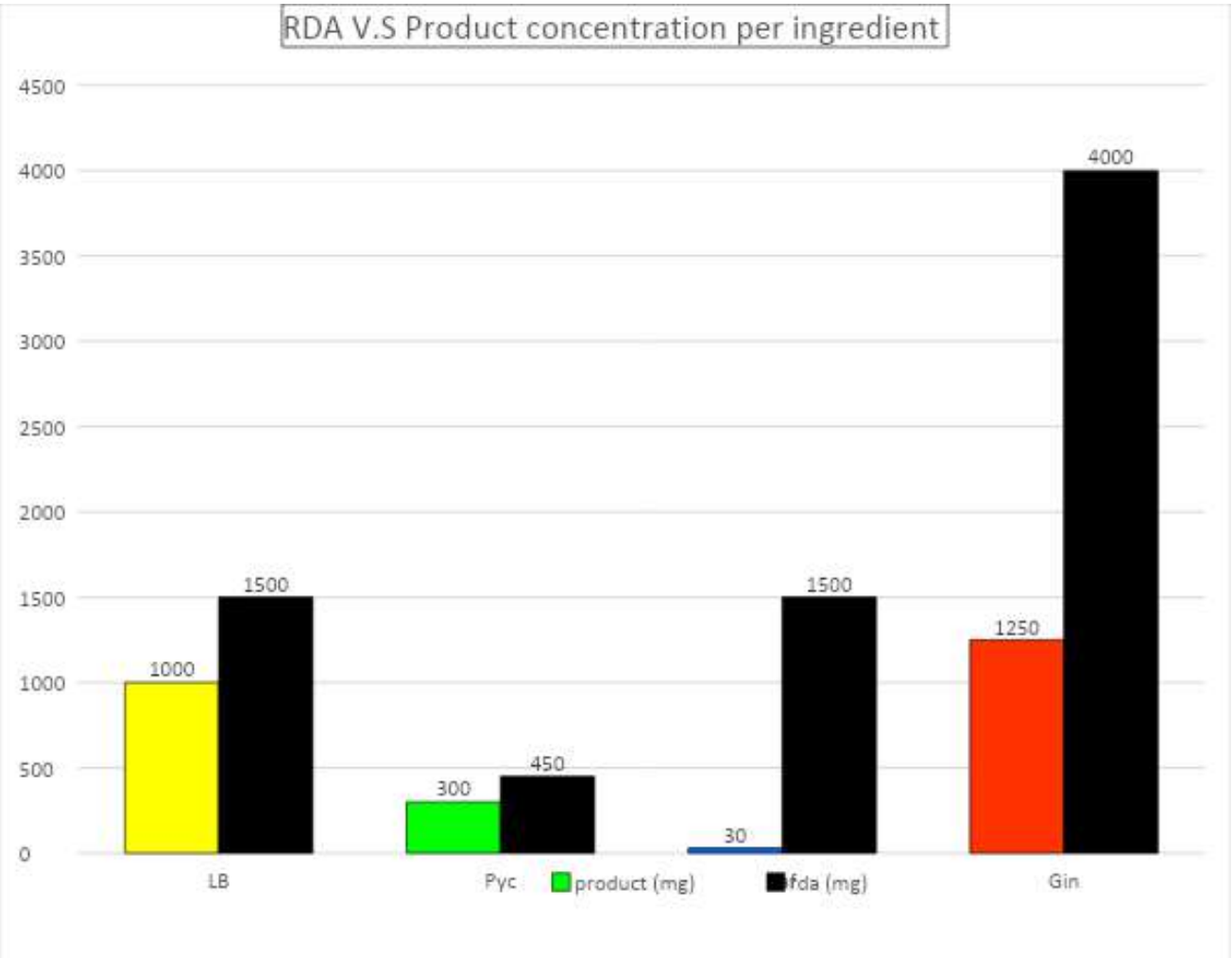

Figure 5: Comparison of Recommended Daily Allowance Concentration With Most Frequently Used Concentrations From Literature Reviews and Experiments. the Lemon Balm in Yellow, Pycnogenol in Green, Saffron in Blue, Ginger in Red. RDA in Black

Histogram with black bars representing the maximum recommended amount that would be safe to ingest, 1500mg of lemon balm was the recommended maximum amount that can be ingested in one day, 450mg of Pycnogenol was the maximum recommended amount that was ingested in one day, 1500mg of saffron was the maximum amount that was safe to ingest in one day no more above this should be ingested, 4000mg or 4g of ginger in the maximum amount that was ingested in one day and this is the highest amount no more than 4000mg of ginger should be consumed or it may cause negative health effects. The yellow bar beside the black bar represents the theoretical amount of lemon balm that would have been used in the PMS product, the green bar represents the theoretical concentration of Pycnogenol that would have been used in the PMS supplement to treat PMS, the small blue bar represents the theoretical amount of Saffron that would have been used in the PMS supplement, and the red bar represents the theoretical amount of ginger that would have been used in the PMS aid product to help treat PMS.

The levels of each concentration per ingredient used was a lot lower in comparison to the RDA of each ingredient. As seen the saffron concentration required was very low in comparison to the RDA.

IV. DISCUSSION

4.1 Pycnogenol and PMS

As mentioned previously Pycnogenol is made from maritime Pine trees (Pinus Pinaster) that grow in southwest France, Pycnogenol is the trademark name for a specific maritime pine bark extract _(WebMD, n.d.). As PMS includes

cramping, muscle pain, abdominal pain and lower back due mostly to inflammation, Pycnogenol has been shown in numerous studies to have anti-inflammatory properties (Raffaella Canalia, 2009) thus ideal for treating PMS pain related symptoms.

4.1.1 Evidence using Pycnogenol in the treatment of PMS

As seen in the figure 4, 36% of the research articles gathered were on Pycnogenol as a treatment for PMS and PMS related symptoms. As mentioned in the method, Pycnogenol is similar to White willow bark (bark from the white willow tree), which contains Salicin which is converted to salicylic acid by the liver. Salicylic acid is a precursor and metabolite of aspirin. The mechanisms of action of white willow bark is like aspirin. White willow bark is an old herbal remedy for pain and inflammation, used as an analgesic and antipyretic agent (Joseph C. Maroon, 2010).

As aspirin has been investigated as it is a pharmaceutical drug sold in many pharmacies and given to many people, the nutraceuticals that are similar or have similar mechanisms to aspirin also have been investigated. As a result of this there are many studies and articles done on Pycnogenol and white willow investigating its beneficial properties and anti-inflammatories properties. Pycnogenol also contains a large amount of phytochemicals, the phytochemicals in Pycnogenol have also been investigated in terms of the beneficial properties which could also be a reason as to why there was more information on Pycnogenol and its effects on the condition PMS.

4.1.2 Optimum Concentration of Pycnogenol

As seen in figure 5, concentrations used in the studied included were ranging from 45mg-300mg across 7 different sources in terms of Pycnogenol reducing PMS, or reducing symptoms related to PMS. To reduce the cramp attacks in athletes 200mg was used, this could be due to its demand of treatment in the body. If there is a large amount of different sites of inflammation, more Pycnogenol was required to treat the different locations. To reduce cramps due to PMS, 60mg was used. This could be due to the location of inflammation being in less places in the body thus less is required. The average concentration used is 134mg, the most frequently used concentration used is 60mg. this suggests Pycnogenol is only required to have beneficial effects on the body at 60mg. It is recommended to take between 50-450mg (WebMD, n.d.) of Pycnogenol per day and no more than 450mg. The studies concluded that as little as 45-60mg can be effective in treating PMS.

4.2 Lemon Balm

Lemon Balm which is also called Melissa officinalis and Balm Gentle is an aromatic herb of the mint family (Lamiaceae) (Petruzzello, 2022). In terms of Phytochemicals, Melissa Officinalis is a plant rich in biologically active compounds which is used worldwide for its therapeutic effects. Studies on its composition have shown that it contains mainly flavonoids, terpenoids, phenolic acids, and tannins. The main active constituents of Lemon balm are volatile compounds such as citronellal and geraniol, triterpenes including oleanolic and Ursolic acid, phenolic acids including caffeic acid and rosmarinic acid, and flavonoids such as quercetin and luteolin (Gabriela Petrisor, 2022).

4.2.1 Evidence using Lemon Balm in the treatment of PMS

As seen in the figure 4, 23% of the research article gathered were on Lemon Balm as a treatment of PMS and PMS symptoms. As the aetiology of PMS is still misunderstood the evidence for the efficiency of herbal medicines on PMS Is limited as the explanation as to how the herb works cannot be explained. The studies involving the use of Lemon Balm are usually involving its effects on anxiety, stress and sleep. PMS symptoms involve low moods, anxiety, stress, and disrupted sleep.

The evidence of the use of Lemon Balm treating the severity of these symptoms proved to be positive, thus making Lemon Balm a supplement to treat PMS and PMS symptoms.

4.2.2 Optimum Concentration of Lemon Balm

As seen in figure 5, Lemon Balm concentrations were ranging from 300mg-1200mg across 5 different sources. Lemon balms most frequent

concentration was 1000mg across the 5 studies, the average concentration was 646mg. The recommended maximum dose is between 900-1500mg daily (Sinai, n.d.). Different studies have used Lemon Balm to investigate its effects on anxiety and stress, for example one study used 600mg on 20 men and women that experience anxiety, 14 of these patients reported full remission of their anxiety disorder (Julien Cases, 2011). In the study involving 1000mg in 2016, the group that received 500mg of lemon balm showed no significant difference to the placebo group in terms of reducing severity of PMS symptoms, the group that received 1000mg showed significant reduce in the severity of PMS. This shows the higher concentration of Lemon Balm used for treating PMS reduced the severity of PMS significantly (Mojgan Mirghafourvand, 2016). Another study using Lemon Balm showed a clear dose dependant effect in improving calmness reducing anxiety with an administered dose of 1600mg being far more effective than 600mg (A.Cernya, 1999). With the most frequent dose used between the 5 studies being 1000mg, this would be the most suitable dosage to treat PMS symptoms to reduce the severity of them.

4.3 Ginger

Ginger root which is an underground stem also known as a rhizome comes from the Zingiber Officinale plant which belongs to the Zingiberaceae family (Britannica, 2022). Ginger is a plant based, whole food spice which can be used in the personal or professional treatment of several different conditions, ranging from gastrointestinal problems to cancer. Turmeric and cardamon is also a member of the family of roots ginger is from. There is evidence for its health benefits as antibacterial/ viral agent, anti-inflammatory agent, antinausea compound, antioxidant, and anticancer (Modi & Modi, 2022).

4.3.1 Evidence of using Ginger to treat PMS symptoms

As seen in the pie chart figure 4, 23% of the research articles gathered were on Ginger as a treatment of PMS, PMS symptoms, and Menstrual related conditions and there symptoms. Ginger has been used for many years as a natural treatment for nausea, pain, gastrointestinal problems and as an antioxidant. There were not many articles directly linking PMS symptom reduction and ginger, although there were many sources using ginger to treat dysmenorrhea as a pain reliever. Ginger has been used as a natural anti-inflammatory and as dysmenorrhea involves inflammation, ginger is a suitable herbal treatment to relieve inflammation. As the aetiology of PMS is understood in comparison to dysmenorrhea the reduction of PMS symptoms by ginger cannot be specifically linked. Research has supported ginger for reducing the severity and duration of nausea and vomiting due to pregnancy, as pregnant women cannot take pharmaceutical medication to relieve nausea ginger has been shown to reduce the severity as an alternative to pharmaceutical medication (authors, n.d.). The number of sources on the use of ginger to reduce PMS symptoms may be low due to the understood aetiology of PMS. Although ginger has been shown to reduce the severity of dysmenorrhea, ginger may also be used to treat PMS symptoms as the symptoms of dysmenorrhea are similar.

Optimum concentration of Ginger to reduce PMS symptom severity, menstrual related symptom severity, and to treat PMS.

As seen in figure 5, Ginger concentrations were ranging from 500mg-1500mg across 5 different sources. The most frequently used concentrations across the 5 different sources was 500mg, the average concentration used of these 5 sources was 975mg. The recommended maximum amount of ginger to consumer per day is 3-4 grams (3000-4000mg), anything more than 6grams of ginger can cause gastrointestinal problems (uclahealth, 2022). The results of a systemic review showed that 750-200mg was effective in reducing the severity of dysmenorrhea but no less than 750mg showed any beneficial properties (James W Daily, 2015). 1000mg should be used in the treatment of PMS and menstrual related symptoms in order to have full effect on reducing the severity of these symptoms, as the average concentration used in these studies was 975mg this should be rounded up to 1000mg to treat PMS.

4.4 Saffron

Saffron is derived from a flower called Crocus Satiuvs as mentioned in the introduction, the flower originated in Greece but is now grown in Iran, Greece, Morocco, and India _(Wikipedia - Saffron , 2023). Saffron is known for one of the most expensive spices in the world, the demand for saffron is increasing worldwide as it plays a role in medicine, cosmetics, and as a spice in food (Loriana Cardone, 2020). Saffron is a herbal product used as an antispasmodic, sedative, a herb to aid digestion, carminative, diaphoretic, soothing pain, and in easing menstruation (Soheila Pirdadeh Beiranvand, 2016). PMS symptoms involve mood swings, depressive episodes due to hormonal level fluctuations, and another symptom of PMS is bloating as mentioned in the introduction. Saffron has been used as an antispasmodic, sedative, and to ease menstrual pain in the past _(Soheila Pirdadeh Beiranvand, 2016) thus making it a suitable nutraceutical active ingredient to use in the PMS supplement to treat these symptoms associated with PMS.

4.4.1 Evidence of Using Saffron in the Treatment of PMS

As seen in the figure 4, 18% of the research article gathered were on Saffron as a treatment of PMS and PMS symptoms. Saffron is a versatile herb in terms of its different functions and different uses, the herb is in high demand due to its versatility, it can be used in medical treatments, cosmetic uses, and as a spice in dishes as mentioned. The price of saffron has increased, the herb is now known as one of the most expensive spices in the world. The price of saffron might explain why there is a lack of experiments using the herb to investigates its beneficial properties in treating PMS. There has been a reduction In the production of Saffron (Loriana Cardone, 2020), this may also be another reason as to why there is a lack of evidence on the treatment of PMS using Saffron although the results of studies done have all been positive in terms of reducing the severity of the symptoms related to PMS. Another reason why there is a lack of experiments using Saffron to treat PMS may be due to the labour required to harvest the crop. The herb has been reported to be an incredibly labour intensive crop to harvest (Riske, 2023).

4.4.2 Optimum Concentration of Saffron Used

As seen in figure 5, there was no range in the concentrations of saffron used in each experiment. Only 30mg of Saffron was required to have a beneficial effect on the symptoms of PMS in terms of alleviating or reducing symptoms according to the 4 studies involved in the results of this study. The reasoning behind the specific amount - 30mg used was not discussed In each study. As mentioned previously as saffron is very labour intensive to harvest, and is in high demand as well as being expensive this may explain the low dosage of saffron used per study. As Saffron is known to have many different health benefits, studies have been done to investigate a safe concentration to ingest. Studies have been done to investigate a safe concentration of Saffron to take as Saffron has been used to treat a variety of diseases and things from mood disorders to a common cold. Saffron supplements are believed to be safe up to 1.5grams per day, these studies have also concluded that benefits of Saffron can be found with as little as 30mg per day which is little in comparison to the maximum dosage 1.5 grams which is also beneficial in cost, as Saffron is the most expensive herb _(staff, 2019).

V. CONCLUSION

The aims of the present study were to investigate if the four nutraceutical active ingredients Pycnogenol, Lemon Balm, Ginger, and Saffron can individually decrease the severity of PMS, or decrease the severity of the symptoms related to PMS. It can be concluded that the ingredients Pycnogenol, Lemon Balm, Ginger, and Saffron can individually and therefore together in a supplement can treat menstrual related conditions, reducing the severity of the symptoms of menstrual related conditions or disorders.

PRISMA (Preferred Reporting Items for Systematic Reviews) was employed to study for four ingredient; Pycnogenol, Ginger, Lemon Balm, and Saffron on reducing PMS symptoms or reducing the severity of PMS. The search was

focused on scientific research articles (Publication years between 1980 and 2022). 22 papers were selected in the analysis regarding the ingredient, concentration, number of people, year of publication, effect of symptom, references and Recommended Daily Allowance (RDA). The 22 papers concluded that these ingredients can reduce PMS symptoms and reduce the severity of PMS related symptoms. The 32 current nutraceutical treatments products for PMS were gathered and evaluated.

23% of the sources concluded that Lemon Balm can treat PMS symptoms, 36% of the sources concluded Pycnogenol can treat PMS symptoms. 18% of the gathered sources concluded that saffron can treat PMS and PMS related symptoms, 23% of the source concluded that Ginger can treat PMS. It can be concluded that Pycnogenol concentrations ranging from 45mg-300mg can be used to treat PMS and PMS related symptoms. It can be concluded that Lemon Balm concentrations ranging from 300mg-1200mg can be used to treat PMS and PMS related symptoms. It can be concluded that Ginger concentrations ranging from 500mg-1500mg can be used to treat PMS and PMS related symptoms. It can be concluded that saffron 30mg can be used to treat PMS and PMS related symptoms. The cost of above concentrations of four ingredients was at rang of market price.

It can be concluded that there are very few supplements available in stores in Ireland that specifically aim to treat PMS or reduce PMS symptoms thus the development of the nutraceutical supplement with Pycnogenol, Lemon Balm, Ginger, and Saffron would be beneficial. The results of the marketing analysis showed there is no product containing just these four ingredients to treat PMS.

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