IN THIS JOURNAL

Great Britain Journals Press

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LONDON JOURNAL OF MEDICAL AND HEALTH RESEARCH

Volume 23 | Issue 4 | Compilation 1.0

COMPILED IN UNITED KINGDOM

ENGLISH

LONDON JOURNAL OF MEDICAL AND HEALTH RESEARCH

Volume 23 | Issue 4 | Compilation 1.0

PUBLISHER

Great Britain Journals Press
1210th, Waterside Dr,Opposite Arlington Building, Theale, Reading
Phone:+444 0118 965 4033 Pin: RG7-4TY United Kingdom

SUBSCRIPTION

Frequency: Quarterly

Print subscription
$280USD for 1 year
$500USD for 2 year
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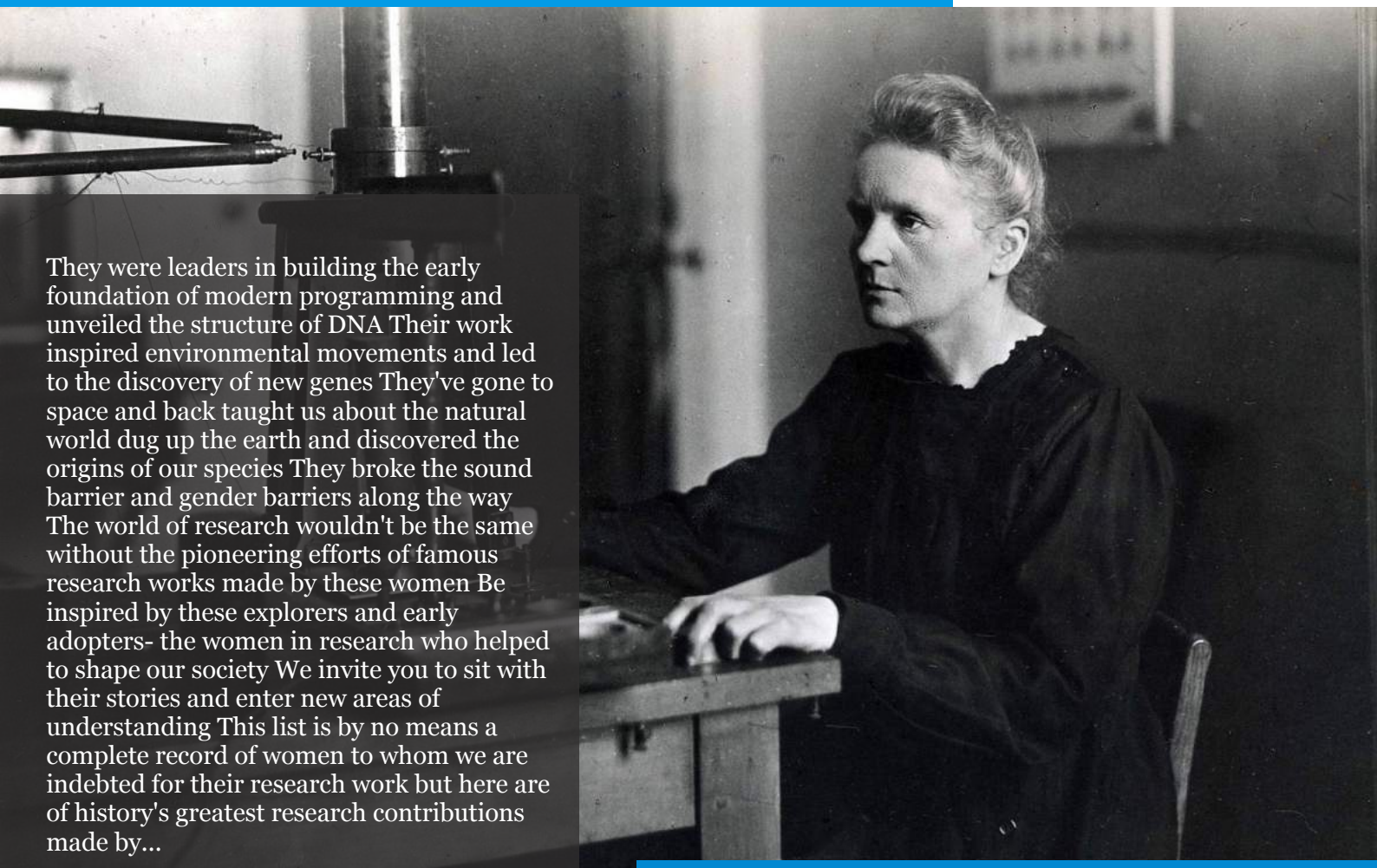

They were leaders in building the early foundation of modern programming and unveiled the structure of DNA Their work inspired environmental movements and led to the discovery of new genes They've gone to space and back taught us about the natural world dug up the earth and discovered the origins of 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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Machine Vision based Unsupervised Summarization of Wireless Capsule Endoscopy Video

Madhura Prakash M & Krishnamurthy G N

ABSTRACT

Wireless capsule endoscopy is a medical procedure that uses a small, pill-sized capsule with a tiny camera inside to examine the inside of the digestive system. The capsule contains a camera that takes pictures as it moves through the digestive tract. The images are transmitted to a small recording device that the patient wears on a belt or shoulder strap. The recording device stores the images, which are later downloaded and examined by a doctor. The pill-sized camera records a video for eight to twelve hours. The purpose of this work is to investigate and put into practise a technique for summarising the capsule endoscopy footage. The method clusters the video frames in order to accomplish this by looking for local maxima in the neighbouring distance graph that is generated from the colour histograms of each video frame. The method then determines the centroid frame for each cluster and produces a key-frame for each cluster. Visualising the conclusion of this investigation is its second objective. This is accomplished by placing each cluster on a timeline according to the size and calibre of the keyframe. The summary of the capsule endoscopy video is generated as a sequence of keyframes. These keyframes are representative frames of the video. The work also proposes a technique to assess the quality and the quantity of the keyframes extracted.

Keywords: wireless capsule endoscopy, video summarization, clustering, key-frames.

Classification: NLM: WN 208.5.C1

Language: English

Great Britain Journals Press

LJP Copyright ID: 392881

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I. INTRODUCTION

Medical endoscopy has developed into an important technique for minimally invasive surgery in recent years. Examination on multiple body areas and for minimally invasive abdominal surgery, joints and other body areas. The term "endoscopy" is derived from the Greek and describes a minimally invasive method of "looking inside" the human body. This is accomplished by inserting a medical device called an endoscope into a hollow organ or body cavity. Depending on the part of the body, it is inserted through a natural body opening or through a small incision that acts as an artificial access. Additional incisions are required during surgery to insert various surgical instruments.

Endoscopy is a catch-all phrase for a wide range of quite varied medical procedures. [1] Endoscopy has numerous varieties, each of which has unique qualities. They can be categorised using a variety of standards, including

- Body part (e.g., abdomen, joints, gastrointestinal tract, lungs, chest, nose)
- Specialty in medicine (e.g., general surgery, gastroenterology, orthopaedic surgery)
- Therapeutic vs. diagnostic focus.

Wireless Capsule Endoscopy (WCE) is a unique form of endoscopy procedure that falls under the diagnostic focus. The patient must swallow a tiny capsule with a built-in camera that transmits a huge number of frames over a prolonged period of time to an external receiver. The doctor then evaluates the footage once this process is complete. WCE is essential for small intestine exams in particular because neither gastroscopy or colonoscopy can access this part of the gastrointestinal tract.

Wireless capsule endoscopy is typically used to examine the small intestine, which is difficult to reach with traditional endoscopy procedures. It is often used to diagnose conditions such as Crohn's disease, celiac disease, and tumours or ulcers in the small intestine. The procedure is non-invasive and painless, and most people are able to go about their daily activities while wearing the recording device.

Capsule endoscopy is a medical diagnostic tool that records video of a patient's digestive tract. The method includes two devices. The first is a capsule with a camera and lights inside. The patient swallows this pill and sends its image to an external receiver. This external receiver is worn by the patient. Capsule endoscopy is used to capture images of the bowel that cannot be reached by conventional endoscopy methods. Capsule endoscopy is used to perform the following diagnostic procedures:

- Recognize inflammatory bowel illnesses; determine the cause of gastrointestinal bleeding.
- Identify cancer.
- Identify celiac illness.
- Look for polyps.
- After additional imaging examinations, perform follow-up testing.

Figure 1: Image of an Endoscopy Capsule

Videos of endoscopic procedures are frequently several hours long. The issue of effective indexing and retrieval is brought on by the enormous amount of video data. It takes time to search through all of these films to find the one you need.

It is difficult to quickly extract the needed information from such a sizable video archive. Hence, methods are required to aid with the difficulty of managing video data. Video summarization is a fundamental method for handling video data.The sample frames from the capsule endoscopy procedure is depicted in Figure 2.

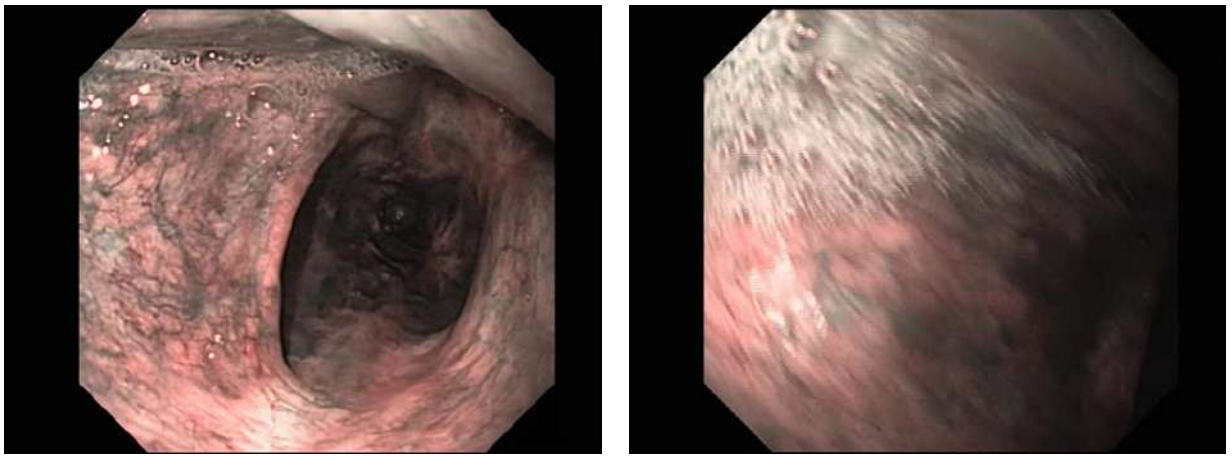

Figure 2: Sample Frames from Capsule Endoscopy Procedure

In order to extract the most important information, known as the keyframe of the video, video summarization attempts to limit the amount of duplicate data. It makes it possible for viewers to swiftly understand the key points of the video. It needs a thorough grasp of the video to produce a synopsis of it. Hence, it is hoped to create a framework that shows the viewer the useful components of video data by taking the information into account.

Video summary messages are typically run using two different approaches: static (keyframe-based) and dynamic (video hover-based) video analytics messages. The static video message contains a collection of a small but significant number of silent frames called keyframes, while the dynamic video message contains a collection of short important video clips. The video summary considers various characteristics such as representativeness, uniformity, static attention, temporal attention, and quality including hue, brightness, contrast, number of colours, edge distribution for keyframe selection. [2]

One of the major problems with capsule endoscopy procedures as mentioned above is that the gastro-intestinal video frames captured in the process are about 8 to 12 hours long. Reviewing the video frames is extremely time consuming for the physicians. The work's major objective is to shorten the time needed for reviewing videos of capsule endoscopy by pointing out the relevant portions of the video to the physician. To achieve this goal this, work aimed at generating a solution for extracting a strip of keyframes that can be presented as a summary of the original video.

With the intent of generating clusters that should be linked to the original video so that the user must be able to easily access the input video frames of every cluster, the two research questions addressed here are:

1. The process of summarising a lengthy capsule endoscopy video in a strip/timeline
2. The process of summarising groups of related frames by a single 'summary'

II. RELATED WORK

Due to the immense amount of video data being generated, there is an increased demand to analyse and summarise them. The work in the domain of video summarization has been carried out for a decade. For summarization, the videos will have to be sampled and divided into segments and shot boundaries. Since the medical videos can be short clippings or full-length videos with no shot-boundaries, extracting key frames is the most challenging task. The key frames can be extracted from the segments based on the several features of the video, either by supervised or unsupervised methods. The key frame extraction may consider low level global features of the video like colour, texture, edges, brightness and so on or the high-level semantics.

A technique for indexing and searching massive amounts of video data is called video summarization. To provide the user with a visual abstract of the video sequence, the approach outputs a brief summary of the video. A good video abstract aims to minimise noise while maximising the amount of information retained in the summary. Clustering techniques are frequently used for automatic video summarization, and they either extract a key-frame or a moving image for each cluster (video skims). In a clustering process, a cluster is a collection of objects that are more similar to one another than they are to the objects in the other clusters (groups). A good cluster will have minimal inter-cluster and intra-cluster variance.

The research study was focused on exploring the solutions available in literature for summarization of endoscopy procedures. The survey in this category consisted of perusing works from [3] to [12].

Ismail et al., [3] had proposed an unsupervised based approach for summarization of WCE videos. Here, the temporal descriptor as well as the colour and texture descriptors were used to represent each video frame. The possibilistic membership values and ideal feature weights inside each cluster were optimised by the authors using a probabilistic clustering and feature weighting technique with an objective function. A mean Jaccard coefficient of 15 had been attained using the technique. Chen et al., [4] had proposed a Siamese Neural Network (SNN) approach and Support Vector Machine (SVM) for summarization of WCE videos. In this approach SNN was used to map. Similar frame pairings were mapped closer using SNN, whereas dissimilar image pairs were mapped farther apart in the feature space.

Euclidean distance measure was computed in order to detect shot boundaries. AN F-measure of 84.75 % was achieved.

Emam et al., [5] had explored and investigated different feature extraction techniques, such as colour histogram, Local Binary Pattern (LBP), and statistical features, a pre-processing phase for WCE images. In this work a cosine similarity distance was computed to summarise the WCE videos and an average reduction rate of 92% was achieved. Lux et al., [6] had clustered similar frames based on low-level image features to extract key frames to summarise arthroscopy videos. Mehmood et al., [7] had proposed a cloud based binary classification model to classify the WCE frames as informative or non-informative.

In another work the authors Mehmood et al., [8] proposed a technique to manage the data generated by WCE procedure. A binary classification approach was proposed to either discard or keep the frame based on colour space conversion, contrast enhancement and curvature measurement.

Lakshmi Priya [9] had proposed a detection process that involved three steps: visual content representation for the feature extraction, construction of continuous signal for similarity assessment between the consecutive frames and the classification of continuity values for Transition identification. A central tendency-based shot boundary detection for video summarization was implemented here. Khan et al., [10] had proposed an ensemble saliency model, consisting of motion, contrast, texture, and curvature saliency for summarization of WCE videos. Sainui [11] had suggested a colour histogram feature and an optimisation method based on the quadratic mutual information statistical dependence measure for increasing coverage of the full video content and reducing redundancy among chosen key frames. For the purpose of summarising echocardiography films, domain-specific knowledge and automatic spatiotemporal structure analysis were integrated by Ebadollahi et al., [12]. Using the graph that was generated, the videos were time sampled.

The survey gave an understanding that the existing solutions focused on extracting statistical features from the individual frames in the video for the purpose of summarization and keyframe extraction. The existing works have not considered the global features of the video and the temporality of the video for summarization purposes. Further, these summarization

techniques were mostly focused on WCE procedure videos.

III. IMPLEMENTATION

Implementation wise the algorithm designed is roughly divided into three parts. These three steps begin with the feature-distance calculation, clustering of the frames, and key-frame extraction from the clusters. The approach combines k-means and local maximum finding. The video frame distances are plotted on a graph. The chi-squared distances between the two-colour histograms of the frames are what these distances represent. The colour histograms have a 4x8x8 bin distribution and are in CIE lab colour space. Then, by looking for the local maxima, it establishes cluster boundaries. These local maxima are discovered with these characteristics. 1. The distance is the greatest distance found after comparing the distances of 2k symmetric neighbours. 2. The distance exceeds the second maximum by an amount n. The closest frame to the cluster mean is chosen by the algorithm to extract a key frame. The proposed algorithm consists of five steps that are depicted in a pipeline like shown in figure 3. The algorithm steps are given in Table 1.

Table 1: Algorithm Steps for Key Frame Extraction

Step 1: Creation of an array of colour histograms. *Step 2*: Calculation of the distance between all consecutive frames and recording them in an array *Step 3:* Cluster Creation *Step 4:* Calculation of keyframe for each cluster *Step 5:* Calculate fidelity of every keyframe

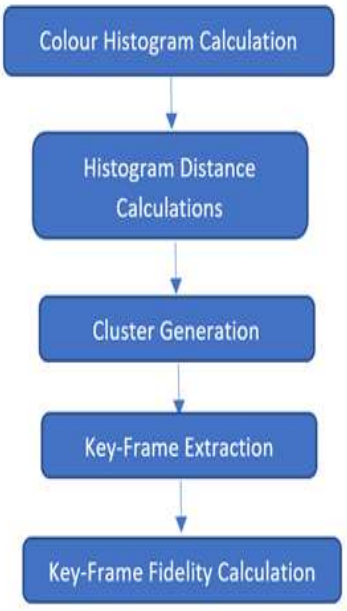

Figure 3: Key-Frame Extraction Pipeline

The colour histograms from the capsule endoscopy video are extracted in the CIE lab colour space. This colour space is preferred, because it excludes the colours from the light intensity. It uses three values to represent colour: L* for perceived lightness and a* and b* for the four distinct hues seen by humans: red, green, blue, and yellow. The histogram has a 4x8x8 stack distribution, resulting in a 20-cell histogram. For each image, a histogram is created and stored in a table. The graph is cached because the graph computation is the slowest part of the algorithm.

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Once stored, they can be reused when calculating keyframe fidelity and when changing settings.

Distance is the similarity metric between two frames that are considered in a cluster. The distances between all consecutive frames in the cluster is computed and stored in the array.

TUsing the Chi-squared test specified in equation 1, the distance between two successive frames is computed using the histograms for the CIE lab colour space.

$$d(C1, C2) = \sum(C1 - C2)^2 / C1 \quad \text{.....(1)}$$

Where C1 and C2 are colour histograms in CIE lab colour space as of two consecutive frames.

Clustering is a method of grouping data points in a data set based on their similarity. The algorithm used here is based on finding local maxima.

Grouping is done according to the distance table. The algorithm covers all calculated distances. It will examine 2 k symmetrical neighbours at each distance point (k neighbours to the left and k neighbours to the right) and determine which neighbours have the highest value. A boundary is established between two points if the current distance is n times greater than the greatest distance between its neighbours (n1).

A key-frame acts as a representative frame that represents a cluster. The mean of the colour histogram is calculated and the frame closest in proximity to the mean histogram is chosen. The resulting key-frames from this technique were not of an optimal quality. The frame that was closest to the mean distance of the cluster's subsequent frames was chosen in the second iteration.

By contrasting a key-frame with the other frames in the cluster, the key-frame fidelity metric expresses the quality of a key-frame. The maximum 15 distances between the key frame and its cluster make up the key frame fidelity. The equation 2 given below is used to calculate the fidelity of the keyframe extracted

$$\text{fidelity}(KeyFr_k, Fr) = \max_i \text{distance}(Fr(i), KeyF_k)\ i = s_k, \ldots e_k \quad \text{..... (2)}$$

Where $KeyFr_k$ is the key frame of cluster k, Fr is the set of frames in the video, s_k is the starting frame of the cluster k, e_k the final frame of the cluster k. The distance function is used to calculate distance between two frames. Keyframe fidelity is calculated so that the user can see the quality of the keyframe relative to other generated keyframes.

IV. RESULTS AND DISCUSSION

For the experiments four test videos with various symptoms are considered from the publicly available dataset Kvasir-Capsule Dataset [13]. The test videos have been resized to a resolution of 256x256. The frames are downsampled at 3 frames per second.

- *Angiodysplasie:* This video consists of 125608 frames.
- *Bleeding:* This video consists of 68939 frames.
- *Polyp:* This video consists of 124970 frames.
- *Ulcer:* This video consists of 121934 frames.

The symptoms in the test set videos considered are explained here. Angiodysplasie, also known as vascular malformation, refers to an abnormality in the blood vessels that can occur in various parts of the body, including the gastrointestinal tract, lungs, brain, and skin. In the gastrointestinal tract, angiodysplasia is a common cause of gastrointestinal bleeding, especially in older adults. It is characterised by the presence of small, dilated blood vessels in the mucosal lining of the intestines, which can rupture and cause bleeding.

A polyp is a growth that projects from the inner lining of a body organ. Polyps can occur in different parts of the body, including the colon, uterus, nasal passages, and stomach. An ulcer, also known as peptic ulcer, is an open sore that can develop in the lining of the stomach or small intestine. It is typically caused by the bacteria

Helicobacter pylori (H. pylori). The sequence of a keyframe strip is shown in Figure 4.

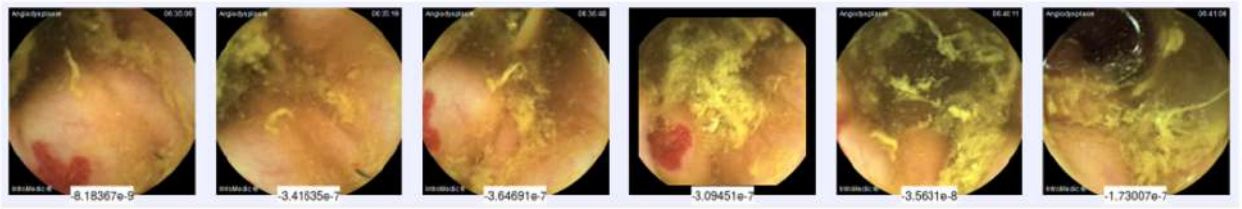

Figure 4: Extracted Key Frame Strip

Experiments have been conducted on all the test videos with the proposed algorithm and the different values for the parameters namely k and n are computed and analysed. The algorithm is tested on all the test videos for assessing the quantity and quality of the key frames. The quantity is measured as the number of frames divided by the total amount of frames in the video in order to compute the compression ratio. The assessment of the quality of the keyframes are done using the mean keyframe fidelities computation. The compression graph of an ulcer video is as shown in Figure 3. Here, the parameter n is represented by the x-axis, the compression rate by the y-axis, and the parameter k by the various lines.

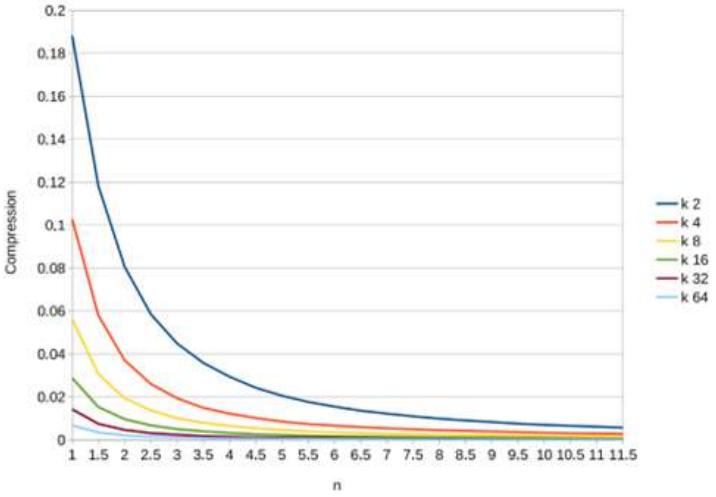

Figure 4: Compression Graph versus n of a test video

The Fidelity graph of the test ulcer video is shown in Figure 4. The distinct lines are the parameter k, the x-axis is the parameter n, and the y-axis is the average fidelity of the key-frames.

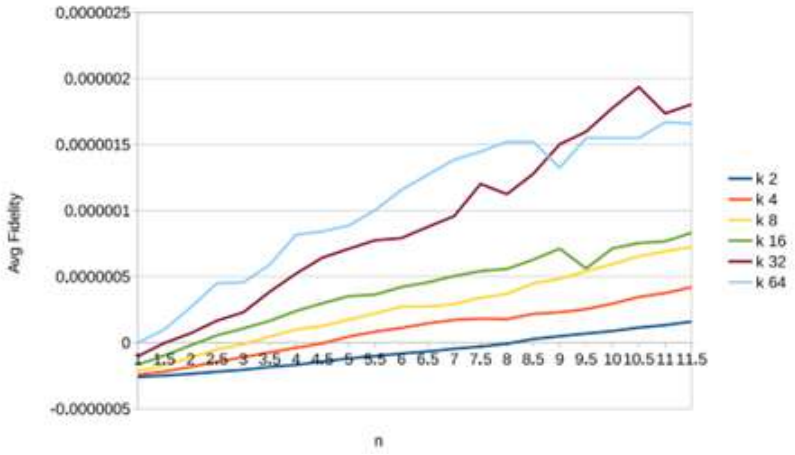

Figure 5: Average fidelity graph of a test video

The compression rate increases similarly to an exponential decay function as the parameters k and n are increased. The key-frame quality degrades roughly linearly as n and k increase. with a little bias in favour of the n-th parameter. This shows that the benefits of compression are diminishing in comparison to key-frame quality.

V. CONCLUSION

The endoscopy video is a special video domain having specific characteristics like specular light reflections, indistinct edges, occlusions, blurriness and artefacts like polyps, smoke, blood, or liquids.

The first two paragraphs can be merged into one Endoscopy videos are content that are unedited having highly similar information, in terms of colour and texture and no shot boundaries.

Endoscopy videos contain a lot of unimportant content like small segments where nothing important happens. It is important and necessary to mine this video content to extract relevant portions that require attention from the physician. This would save the physician's time to a great extent. In this work the spatial features of the video frame namely the histogram distribution in CIE colour space has been considered for key frame extraction. The key frame extraction pipeline has been designed and implemented and the quantity and the quality of the frames extracted have been assessed. Since the video data consists of both spatial and temporal features it is important to consider both of these features in order to generate more meaningful summaries. Further work in summarization of endoscopy video should consider both spatial and temporal features.

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ABSTRACT

Acne is one of the most common skin pathologies, one of the causes is Propionibacterium acnes, an anaerobic and gram-positive microorganism that lives in the hair follicles of the skin, currently presents resistance to antibiotic based treatments; this research topic has the purpose of evaluating the antibiotic activity of Cannabidiol oil against Propionibacterium acnes, Staphylo- coccus aureus and Staphylococcus epidermidis and the level of toxicity against Artemia salina.

For the methodology, antibiograms were used by the Kirby-Bauer method, where the concen- trations were evaluated: 0,8 %; 0,6 %; 0,4 %; 0,3 % and 0,1 %; Amoxicillin for positive control and Dimethyl sulfoxide (DMSO) for negative control; the percentage of inhibition against Propioni- bacterium acnes and two control bacteria were calculated: Staphylococcus aureus and Staphylo- coccus epidermidis. Once the percentage of inhi-bition was tested, a toxicity study was carried out against Artemia salina to determine its LD50.

Keywords: CBD, antibiograms, bioassay, LD50.

Classification: LCC Code: QV 735

Language: English

Great Britain Journals Press

LJP Copyright ID: 392882

London Journal of Medical and Health Research

Volume 23 | Issue 4 | Compilation 1.0

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Acne is one of the most common skin pathologies, one of the causes is Propionibacterium acnes, an anaerobic and gram-positive microorganism that lives in the hair follicles of the skin, currently presents resistance to antibiotic based treatments; this research topic has the purpose of evaluating the antibiotic activity of Cannabidiol oil against Propionibacterium acnes, Staphylococcus aureus and Staphylococcus epidermidis and the level of toxicity against Artemia salina.

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The Cannabidiol oil obtained from the Ecuadorian company was used as the antibiotic agent to be evaluated, and it was found that at a concentration of 0,8% it presented a percentage of inhibition of 91,2 %; 98,7 % and 93,6 % against Propionibacterium acnes, Staphylococcus aureus and Staphylococcus epidermidis, respectively, data that do not present a significant difference against amoxicillin; for the Artemia salina test, a LD50 of 4,8 % was obtained; taking into account that the commercial oil has a presentation of 1,6 % (500 mg/30 mL), it results in a relatively innocuous product. Thus concluding that Cannabidiol oil is a very promising antibiotic due to the inhibition percentages presented and low toxicity.

Keywords: CBD, antibiograms, bioassay, LD50.

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I. INTRODUCTION

The use and abuse of antibiotics not only in Ecuador but worldwide, is a fashionable and controversial topic, due to the efforts made by professionals, this is a practice that continues to leave in its wake several serious and irreversible consequences. One of them is the bacterial resistance acquired by microorganisms to antibiotics. Several resistances of Propionibacterium acnes have been reported over the years, as is the case of Clindamycin and Erythromycin, which were reported in 1979, and later in 1983 the first resistance to tetracycline was reported [10].

It has been reported in patients with severe acne, that 70 % of them present high biofilm formation and multi-resistance of Propionibacterium acnes to various antibiotics. For this reason, it is interesting to use new alternatives against. It has been reported in patients with severe acne, that 70 % of them present high biofilm formation and multi-resistance of Propionibacterium acnes to various antibiotics. For this reason, it is interesting to use new alternatives against Propionibacterium acnes, it has been reported in studies [5,11] that the use of Cannabidiol, works excellent with biofilms of gram-positive microorganisms; therefore, studying the effect of

Cannabidiol against Propionibacterium acnes is promising.

II. MATERIALS AND METHODS

Cannabidiol oil was obtained from an Ecuadorian company, in a 500 mg/30mL presentation. The bacterial strain of Propionibacterium acnes ATCC 11827; Staphylococcus aureus ATCC 29213 and Staphylococcus epidermidis ATCC 14990 were obtained from the Cryobank of the Life Sciences Laboratories of the Salesian Polytechnic University. The manual described by [20] was used as a reference and the tubes containing the bacterial beads were thawed, with a punch to perform the striation in triplicate throughout the petri dish.

The recommendations of [7] were followed to prepare dilutions with oils and dimethyl sulfoxide. Five oil-based dilutions were prepared at concentrations of 0.1 %; 0.3 %; 0.4 %; 0.6 % and 0,8 % whose solvent was DMSO; the final volume for each dilutions was 5 mL in every amber bottle.

A commercial antibiotic (Amoxicillin) was taken as a positive control, which is a betalactam antibiotic used for both gram-positive and gram-negative bacteria, due to its broad spectrum of bacterial activity [1]. This antibiotic is used for antibiotic testing in the Staphylococcus and Propionibacterium families, because of their sensitivity to its compounds [8,10].

P. acnes was incubated in TSB medium under anaerobic conditions at 35 °C for 16 hours, for S. aureus and S. epidermidis were incubated in TSB medium at 37 °C in an incubator.

After the established time passed. It was centrifuged at 350 rpm for 20 minutes, the supernatant was discarded in a beaker with alcohol, the bottom of the bacterial biomass was conserved, sterile saline was added to each tube and vortexed for 2 minutes until reaching the 0,5 McFarland scale and read in the JASCO V-730 spectrophotometer with the spectra manager TM software until reaching an absorbance of 0,200 at 655 nm, obtaining an inoculum of 106 CFU/mL.

500 µL of bacterial inoculum was taken, dropped in the center of the Petri dish with Muller Hinton [15]. One disc of antibiotic Amoxicillin was placed as positive control, one blank disk with DMSO as negative control and 5 blank discs with the respective dilutions from Cannabidiol oil, which would be at concentrations of 0,1 %; 0,3 %; 0,4 % 0,6 % and 0,8 % in a volume of 20 µL. Petro dishes with S. aureus and S. epidermidis were placed in an incubator at 37°C for 24 hours; P. Acnes was incubated in anaerobiosis at 35 °C.

When the time of 24 hours in the incubator for S. aureus, S. epidermidis and P. acnes had passed, each Petri dish was checked to with a caliper ruler.

The percentage of inhibition of each bacterium with respect to each concentration was calculated using the following reference formula (1) from [9].

7 grams of A. salina eggs were obtained from a commercial house, 2 g of egg were weighed, hydrated for 30 min with distilled water, then 25 mL of sodium hypochlorite were added (4 replicates), the eggs were recovered and rinse with distilled water. For the incubation, a 3 liter bottle was used, 1500 mL of 2 % salina water was added, pH 8, temperature 24 °C and constant aeration for 48 hours 22.

To make the emulsions with Cannabidiol (CBD) oil, a 1:1 ratio of oil and tween 80 was used a co-emulsifier used in the cosmetic and food area due to its low toxicity level and according to the work carried out by [15] it is considered innocuous with Artemia. Cannabidiol oil was used to obtain emulsion at 3.2 %; 1.6 %; 0.8 %; 0.4 % and 0.2 % with which we worked in test tubes with A. salina to determine the LD50.

After 24 hours of incubation, dead nauplii were counted using a NIKON SMZ745 stereoscope, where those that did not show any seconds were considered dead.

III. RESULTS

Table 1: Determination of the antibiotic activity of Cannabidiol oil against P. acnes.

Bacteria	Concentration	$\underline{X}$	% inhibition
P. acnes	0,8	1,9	91,2
	Control +	2,0	100

1 Average halo and percentage inhibition of cannabidiol oil against P. acnes

The percentage of inhibition for P. acnes is 91.2% at a concentration of 0.8% of Cannabidiol oil, which gives a high percentage of inhibition compared to a commercial antibiotic, Amoxicillin, supporting of inhibition compared with a commercial antibiotic, Amoxicillin, supporting the alternative hypothesis showing that Cannabidiol oil inhibits P. acnes.

A Tukey study showed that there is an important group of data, in which their averages are not significantly different; the group is formed by the positive control (commercial antibiotic), CBD5 (0.8% Cannabidiol oil).

Table 2: Determination of the antibiotic activity of cannabidiol oil against S. aureus

Bacteria	Concentration	$\underline{X}$	% inhibition
S. aureus	0,8	1.7	98.7
	Control +	1.8	100

2 Average halo and percentage inhibition of cannabidiol oil against *S. aureus.*

The concentration of Cannabidiol oil at 0.8 % has an inhibition percentage of 98.7 %, a value very close to the positive control which was the commercial antibiotic Amoxicillin.

With a Tukey test it was proved that there is a group of interest where their averages are not significantly different, the group is formed by the positive control (antibiotic Amoxicillin) and CBD5 (0.8% Cannabidiol oil).

Table 3: Determination of the antibiotic activity of cannabidiol oil against S. epidermidis

Bacteria	Concentration	$\underline{X}$	% inhibition
S. epidermidis	0,8	1.8	93.6
	Control +	1.9	100

3 Average halo and percentage inhibition of cannabidiol oil against S. epidermidis

The results show that the percentage of inhibition for S. epidermidis with 0.8 % oil was 93.6 %, affirming the alternative hypothesis on the inhibition of Cannabidiol oil against S. epidermidis.

The Tukey test shows that there is an important group where the positive control (Amoxicillin) and CBD5 (0.8 % Cannabidiol oil) are grouped together. As a result, we would obtain that the 0.8 % Cannabidiol oil is similar in inhibition to the positive control (Amoxicillin) supporting the alternative hypothesis that there is at least one concentration that inhibits S. epidermidis.

3.1 Toxicity test

Dilutions of Cannabidiol oil were made at the intervals of: 3.2 %; 2.8 %; 2.4 % 2.0 %. In order to determine the lethal dose, a linear regression was performed and an LD50 of 4.86 % (48 mg/mL) was obtained.

3.2 Formatting of Mathematical Components

$$Inhibitory\ effect = \frac{Inhibition\ halo\ diameter}{positive\ control\ halo\ diameter} * 100$$

IV. DISCUSSION

In accordance with the studies of [18] where he mentions that *Cannabidiol* has a potential antimicrobial activity against gram-positive bacteria, such as *P. acnes* with which, using it could be beneficial for the treatment of acne vulgaris. *Cannabidiol* has a potential role as an antimicrobial agent [22], it was demonstrated through clinical studies that *Cannabidiol* oil acts on sebocytes, thus having an anti-acne function, controlling sebum production, mitigating the inflammatory process and functioning as a bactericidal agent by reducing bacterial proliferation [4,21].

Cannabidiol oil inhibits *S. aureus*; the results obtained by [2] can be compared with those of this work since *Cannabidiol*, one of the main cannabinoids of the plant showed a potent activity against the strain *S. aureus*.

The results obtained from the test with *S. epidermidis* can be compared with the study conducted by [19], where the mechanism of action of *Cannabidiol* in causing the death of gram-positive bacteria was evaluated, due to the ability of this compound to inhibit the release of vesicles from the bacterial membrane; these vesicles are extremely important for cell communication and pathogen-host interaction.

In the negative control of the toxicity test with *Artemia salina*, saline water was used, there was no dead individual so that the test is validated as there are no natural factors that can kill the study individuals; as indicated by [24, 13]; the percentage of mortality in the negative controls did not exceed 10 %. In the positive control where 96% alcohol was used, it was confirmed as an adequate positive control since the death of the individuals in the study was confirmed as indicated by the study of [23].

The use of *Cannabidiol* oil at concentrations from 2 % onwards gradually increases the number of dead *A. salina* [14]. A plant oil when exceeding a LC50 of 1000 ppm in bioassays with *A. salina* does not have a high degree of toxicity, due to the ability of the nauplii to present a very thin cuticle, which makes them sensitive to toxicants in the medium, which penetrate through the physiological barriers and are rapidly absorbed [6, 25].

V. CONCLUSIONS

The valued Cannabidiol oil was obtained from an Ecuadorian company, which presents a concentration of 500 mg/30mL. evaluation by means of the HPLC technique.

Cannabidiol oil showed antibacterial activity with halo averages of 1.8 cm; 1.7 cm and 1.8 cm for Propionibacterium acnes, Staphylococcus aureus and Staphylococcus epidermidis respectively at a concentration of 0.8 %, compared to the control antibiotic (Amoxicillin) with 2 cm of halo, by means of the statistical analysis it was possible to reject the null hypothesis and accept the alternative since Cannabidiol oil inhibits Propionibacterium acnes, Staphylococcus aureus and Staphylococcus epidermidis with the proposed concentrations. Likewise, the alternative hypotheses for the analysis of variance and Tukey are accepted, at least one degree of concentration of Cannabidiol oil inhibits the 3 bacteria with a similar effect to Amoxicillin. At the end of the experimental work, it was concluded that the results obtained under the laboratory test show that the use of Cannabidiol oil is effective for the control of the mentioned bacteria and it is a promising field for possible elaboration of phytoproducts for human use in order to improve and provide all the benefits offered by Cannabidiol oil.

For the toxicity bioassay where Artemia salina was used, a LD50 value of 4.8 % was obtained, which showed that the commercial Cannabidiol oil in a 500 mg/30mL presentation, equivalent to 1.6 %, is a relatively innocuous product at the highest concentration and non-toxic at very low

concentrations. Although at higher concentrations survival may be negatively affected by swimming problems, the results confirmed the alternative hypothesis that the concentration of Cannabidiol oil is directly proportional to the percentage of mortality of Artemia salina.

Author Contributions: "Conceptualization, Grace Pila and Danny Segarra.; methodology, Grace Pila, and Danny Segarra.; software, Danny Segarra..; investigation, Grace Pila and Danny Segarra.; writing—original draft preparation, Grace Pila and Danny Segarra.; supervision, Marco Cerna; funding acquisition, Grace Pila and Danny Segarra. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

ACKNOWLEDGMENTS

Our most sincere thanks to the technical team of the life sciences laboratories of the Salesian Polytechnic University, to our friends, colleagues and family.

Conflicts of Interest: The authors declare no conflict of interest.

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Some Egyptian Medicinal Plants and Heart, and Blood Disease

Mohammed Sayed Aly Mohammed

ABSTRACT

Many medicinal plants have a significant effect upon the diseases, such as diabetes, skin, liver cancer, heart, respiratory, blood, and nervous system. Medicinal plants in Egypt contain a high concentration of secondary metabolites, according to suitable environmental conditions. The ancient Egyptians had written a lot of information about medicinal plants, their uses, and many drugs of these medicinal plants still used in medicine. Many medicinal plants are cleared on the wall of temples and in the papyri, famous Ebers papyrus that is written in 1550 B.C. cardiovascular diseases (CVD) defined according to the World Health Organization (WHO) as a defect of the circulatory system including heart and blood vessels. There are many types of CVD such as coronary heart disease (CHD), cerebrovascular disease, heart attacks, and strokes. The deposition of fatty substances, cellular waste, cholesterol, and other substances on the inner walls of blood vessels is the major cause of CVD, World Health Organization (2014). The aim of the present study is to clarify some Egyptian medicinal plants for heart and blood diseases such as Tropaeolum majus L. Uriginea maritima (L.), Salvia Species, Allium cepa and Allium sativum. The location, chemical components, active ingredients, and position of the effect of previous plants.

Keywords: NA

Classification: LCC Code: QK99.A1

Language: English

Great Britain Journals Press

LJP Copyright ID: 392883

London Journal of Medical and Health Research

Volume 23 | Issue 4 | Compilation 1.0

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I. INTRODUCTION

Traditional medicinal plants definite a Phyto-remedies, their use still burgeoning worldwide, the medicinal plants are used as a herbal for recovery to many diseases, and of their constituents now used in very most beige scale to cure of many diseases such as diabetes2, skin, liver, cancer and heart disease too. Drugs of herbal or their derivatives are considered natural products that mostly have not no side effects.

Medicinal plants contain many compounds, which have an excellent effect on remedies for many diseases, such as essential oils that are used as a sedative, skin diseases, relaxing, and so on.

Phenols and flavonoids that are used as an antioxidant that prevents cancer, glyoxidates that have a good effect upon heart disease such as quercetin of onion, scillaren of white squill, allyl of garlic and so on of the contents of medicinal plants that the spot will be light on their active ingredients for heart disease in the present work.

The heart attack returns to the of heart muscle, then the coronary artery is blocked, that supplies blood to the heart, that due to damage of heart muscle sustenance, and cause that blood is not arrived to it, so it becomes starved of Oxygen.

Systolic heart failure done, because the heart muscle could not push blood around all the body properly. At the time of the heart and blood circulation both stop cardiac arrest, so a person's life will end.

The factors that cause heart failure are type 2 diabetes, smoking, anemia, obesity, lupus, thyroid problems, includes hyperthyroidism and hypothyroidism, inflammation of heart muscle that returns to the virus, and could drive to failure of the left side of heart. Abnormal heart rhythms and fast heartbeat could cause heart weakness, and so on a slow heartbeat due to reduced blood flow, which leads to heart failure.

Dietary factors are very close to heart coronary, particularly when dietary contains the greatest

ratio of saturated fatty acids, Coronary heart disease is considered number one that causes death in the world. However, it must be said that most people survive their first heart attack and return to their normal lives, enjoying many more years of productive activity. But experiencing a heart attack does mean that you need to make some changes.

Garlic (Allium Sativum)

Garlic is a perennial plant; it has been valued for its medicinal properties. As an herbal medicine, it has been more closely examined than many other herbs. Research focuses on garlic for preventing atherosclerosis. Multiple beneficial cardiovascular effects were found, including lowering of blood pressure, inhibition of platelet aggregation, enhancement of fibrinolytic activity, lowering of cholesterol and triglyceride levels, and protection of the elastic properties of the aorta (Rahman and Lowe 2006).

The intact cells of garlic bulbs contain an odorless sulfur-containing amino acid, allinin. When garlic is crushed, allinin is exposed to alliinase, which converts allinin to allicin. This has potent antibacterial properties and is highly odoriferous and unstable. Ajoenes are the self-condensation products of allicin and suggested to be responsible for garlic's antithrombotic action. Most authorities now agree that allicin and its derivatives are the bioactive constituents of garlic.

Dried garlic preparations lack allicin but contain both allinin and allinase. Since allinase inactivated in the stomach, dried garlic preparations should have an enteric coating so that they pass unaltered through the stomach to the small intestine, where allinin enzymatically converted to allicin. Only a few commercially available garlic preparations standardized for their yield of allicin based on the allinin content (Mashour, Lin, and Frishman 1998).

The consumption of large quantities of fresh garlic (0.25-1.0 g/kg or about 5-20 average-sized 4 g cloves) found to produce the aforementioned beneficial effects (Kleijnen, Knipschild, and ter Riet 1989). In support of this, a double-blind, crossover study of moderately hypercholesterolemic men, which compared the effects of 7.2 g of aged garlic extract with placebo on blood lipid levels, found a maximal decrease of 6.1% in total serum cholesterol levels and 4.6% in LDL cholesterol levels with garlic (Steiner et al. 1996).

However, despite the positive evidence from a number of trials, full endorsement of garlic for CVD prevention is not currently possible. Many published studies have methodological shortcomings (Isaacsohn et al. 1998). Trials were small, lacked statistical power, had inappropriate methods of randomization, lacked dietary run-in periods, were of short duration, or failed to undertake intention to treat analysis. This has led to a cautious approach to previous meta-analyses (Neil et al. 1996). One more recent meta-analysis concludes that garlic decreases total cholesterol to a modest extent, an effect driven mostly by the modest decreases in triglycerides, with no appreciable effect on LDL or HDL cholesterol (Reinhart et al. 2009).

Garlic studied hypertension with no conclusive result (Simons, Wollersheim, and Thien 2009). A meta-analysis of eight trials suggested some clinical value in patients with mild hypertension, but the evidence was insufficient to recommend garlic for routine clinical therapy (Silagy and Neil 1994). Garlic reported to show antiplatelet stickiness activity. This has been documented in vitro (Bordia, Verma, and Srivastava 1996), and another study examined the effect of consuming a clove of fresh garlic on platelet thromboxane production. After 26 weeks, serum thromboxane levels lowered by about 80% (Ali and Thomson 1995). In these ways, garlic is beneficial to cardiovascular health, and these effects need further study. However, with consumption of more than five cloves daily, heartburn, flatulence, and other gastrointestinal disturbances reported.

Allergic contact dermatitis is also reported, and patch testing is available when garlic allergy suspected (Delaney and Donnelly 1996). Due to its antithrombotic activity, garlic is taken with caution by people on oral anticoagulants (Rose et al. 1990).

Onion (Allium cepa L.)

The onion (*Allium cepa* L.), is known as the bulb onion or common onion, onions are cultivated and used around the world. Most onion cultivars are about 89% water, 9% carbohydrates (including 4% sugar and 2% dietary fiber), 1% protein, and negligible fat (table). Onions contain low amounts of essential nutrients and have an energy value of 166 kJ (40 Calories) in a 100 g (3.5 oz.) amount. Onions contribute savory flavor to dishes without contributing significant caloric content (US National Onion Association, 2011)

Considerable differences exist between onion varieties in phytochemical content, particularly for polyphenols, with shallots having the highest level, six times the amount found in Vidalia onions. Yellow onions have the highest total flavonoid content, an amount 11 times higher than in white onions *(*Slimestad, et al., 2007), they added that red onions have considerable content of anthocyanin pigments, with at least 25 different compounds identified representing 10% of total flavonoid content.

Allium cepa is highly valued for its therapeutic properties. It was used as a food remedy from time immemorial. Research shows that onions may help guard against many chronic diseases. That is probably because onions contain generous amounts of the flavonoid quercetin. Studies have shown that quercetin protects against cataracts, cardiovascular disease, and cancer. In addition, onions contain a variety of other naturally occurring chemicals known as organosulfur com-pounds, which, linked to lowering blood pressure and cholesterol levels. Although rarely used specifically as a medicinal herb, the onion has a wide range of beneficial actions on the body and when eaten (especially raw) on a regular basis will promote the general health of the body. The bulb is anthelmintic, anti-inflammatory, antiseptic, antispasmodic, carminative, diuretic, expectorant, febrifuge, hypoglycaemic, hypotensive, lithontripic, stomachic and tonic.

When used regularly in the diet it offsets tendencies towards angina, arteriosclerosis and heart attack. This is used particularly in the treatment of people whose symptoms include running eyes and nose. The onions ability to relieve congestions especially in the lungs and bronchial tract is hard to believe until you have actually witnessed the results. The drawing of infection, congestion and colds out of the ear is also remarkable. The onion will relieve stomach upset and other gastrointestinal disorders and it will strengthen the appetite. Pharmacologically known as *Allium cepa*, onion found in every household. The purple-skinned onion tastes great.

Additionally, it has several health benefits and is part of many home remedies and beauty solutions.

Onion possesses properties allied to those of garlic, but in a milder degree, and the absorption of its oil and influence upon the system is somewhat similar to that of the oil of garlic.

Onions do not agree with all persons, especially dyspeptics, in whom they favor the production of flatus, which, however, is a common symptom among all those who eat largely of them; boiling, in a great measure, deprives them of this property. Sugar and onion-juice form a syrup, much used in domestic practice, for *cough* and other affections of the air-tubes among children. A roasted

Onion employed as a cataplasm to support tumors, or to the ear in *otitis* has proved beneficial. A saturated tincture of onions made with good Holland gin, found serviceable in *gravel* and dropsically affections. A cataplasm of onions pounded with vinegar, applied for a number of days, and changed 3 times a day, has been found to cure corn and bunions. Most human studies that have shown an effect from onions used at least 25 grams per day and often two to four times that amount. Though some studies have found cooked onions acceptable, several studies suggest that onion constituents degrade by cooking and that fresh or raw onions are probably most active. If a tincture, syrup, or oil extract is used, 1 tablespoon three times per day may be necessary for several months before effects are noted.

Due to the anti-inflammatory agents in onions they help reduce the severity of symptoms associated with conditions such as the pain and swelling of the osteo and rheumatoid arthritis, the allergic inflammatory response of asthma, and the respiratory congestion associated with common colds. The onions have anti-inflammatory effects only due to their vitamin C and quercetin, but other active components called isothiocyanates have made onions a good ingredient for soups and stews during cold and flu season. WHO recommends the use of fresh onion extracts for treating coughs, colds, asthma, bronchitis and relieving hoarseness. The World Health Organization also supports the use of onions for the treatment of appetite loss and preventing atherosclerosis. Similar to garlic, the regular consumption of onion lowers blood pressure and the serum levels of cholesterol and triglyceride, while increasing HDL levels. As a result, it prevents atherosclerosis and diabetic heart disease, and reduces the risk of heart attacks or strokes. Onions considered as one of the small number of vegetables, which reduce heart disease risk. This beneficial effect attributed to its vitamin B6, which lowers homocysteine levels, an important risk factor for heart attacks and strokes. Onions are natural anti-clotting agents due to their sulfur content. In ancient Greece, large quantities of onion consumed in order to lighten the balance of blood. The high amount of fructo oligosaccharide in onions stimulates the growth of healthy bacteria and suppresses the potentially harmful bacteria in the colon such as Bacillus subtilis, Salmonella, and E. coli. Sulfides in onion extracts provide protection against tumor growth especially stomach and colon cancer.

Roasted onions are good for earaches. They also recommended treating headaches, snakebites, hair loss and infertility in women. In many parts of the world, onions used to heal blisters and boils. Products containing onion extract (such as Mederma) used to treat scars; they also relieve itching secondary to allergy. In homeopathy, *Allium cepa* used for rhinorrhea and hay fever.

Onions believed to be effective in diabetes. Its Allyl propyl disulfide and chromium can decrease fasting blood glucose levels, improve glucose tolerance, and lower insulin levels. Onions may be especially beneficial for women, who are at creased risk of osteoporosis during the menopause. Onion's gamma-L-glutamyl-trans-S-1-propenyl-L-cysteine sulfoxide (GPCS) inhibits the osteoclasts (the cells which break down bone) activity and fights osteoporosis. Onion syrup is useful in extracting renal stones. Onions are also a recommended treatment for edema due to their diuretic effect. They also promote the menstrual periods.

Salvia species

The genus Salvia (sage) belongs to the Lamiaceae and encompasses 900 species worldwide of which ca. 26 indigenous species found in Africa. Salvia is the largest genus in this family and constitutes almost one quarter of the Lamiaceae. Salvia species used in many parts of the world to treat various conditions. Many sages, if not all, form an integral part of traditional healing in Africa, particularly in Sinea where they occur in abundance. Several species used to treat microbial infections, cancer, malaria, inflammation, loss of memory and to disinfect homes after sickness.

The composition of the oils from leaves and flowers of three Salvia species (S. aethiopis L., S. hypoleuca Benth. and S. multicaulis Vahl.) has been analyzed by a combination of GC and GC–MS. During the flowering period, two oils (S. aethiopis and S. hypoleuca) consisted mainly of sesquiterpenes, while in S. multicaulis oil mono-terpenes predominated over sesquiterpenes. The major components of the oil of S. aethiopis were β-caryophyllene (24.6%), α-copaene (15.5%) and germacrene D (13.5%). In the oil of S. hypoleuca, β-caryophyllene (22.0%), δ-elemene (15.5%) and bicyclogermacrene (15.1%) were found to be the major constituents. α-Pinene (26.0%), 1,8-cineole +limonene (20.0%) and camphor (19.0%) were the predominant compounds in the oil of S. multicaulis.

Ten phenolic compounds were isolated from butanol fraction of sage extracts, and their structures were determined with spectral methods (NMR, MS, IR), among them a novel compound,

4-hydroxyacetophenone-4-o-β-D-apiofuranosyl-(1 ___6)-o-β-D-glucopyranoside, was identified.

The rosmarinic acid and luteolin-7-o-β- glucopyranoside were the active compounds of antioxidantactivity.

The metabolite profile of S. miltiorrhiza (SM) or Chinese sage is similar to that of common sage, and recently, it was shown that an extract of SM was able to lower the plasma cholesterol, low density lipoprotein (LDL), and triglycerides (TGs), as well as increase the high density lipoprotein (HDL) levels in lipidemic rats (Christensen, et al., 2010).

The extract of S. officinalis is found to activate peroxisome proliferator-activated receptor gamma (PPARγ) which is a regulator of genes involved in energy spending as well as lipid and glucose metabolism, and its activation improves the HDL/LDL ratio and lowers TGs in serum, reduces insulin resistance, and reduces the size of adipose (fat) tissue (Christensen, et al., 2010). Extracts from some sage species shown to be effective in the prevention of cardiovascular disease due to, at least in part, prevention of LDL-cholesterol oxidation (Ramos, et al., 2009).

Tropaeolum majus

The garden nasturtium (*Tropaeolum majus* L.) belongs to the family Tropaeolaceae. Native to South America it brought to Europe in the XVI century. It is a plant with numerous healing properties. Medicinal plants such as the garden nasturtium contain trace elements and bioactive compounds, which easily absorbed by the human body. The flowers and other parts of the garden nasturtium are a good source of microelements such as potassium, phosphorus, calcium and magnesium, and macro elements, especially of zinc, copper and iron. The essential oil, the extract from the flowers and leaves, and the compounds isolated from these elements have antimicrobial, antifungal, hypotensive, expectorant and anticancer effects. Antioxidant activity of extracts from garden nasturtium is an effect of its high content of compounds such as anthocyanins, polyphenols and vitamin C. Due to its rich phytochemical content and unique elemental composition, the garden nasturtium may be used in the treatment of many diseases for example the illnesses of the respiratory and digestive systems.

High content of erucic acid in nasturtium seeds makes it possible to use its oil as treatment in adrenoleukodystrophy. It is also applied in dermatology because it improves the condition of skin and hair. More recently, the flowers of this species used as a decorative and edible element of some types of dishes.

It is used in folk medicine against cardiovascular disorders, urinary tract infections, asthma, and constipation (Ferro, 2006). Previous phytochemical studies have reported the occurrence of the flavonoids isoquercitrin and kaempferol glycoside, in the leaves of *T. majus* (Zanetti et al., 2004), besides glucosinolates and tetracyclic triterpenes (Griffiths et al., 2001). Several studies disclosed a number of relevant pharmacological properties associated with flavonoids, such as antioxidant, diuretic and cardioprotective effects (Wu and Muir, 2008).

Diuretics, such as thiazides and furosemide, are among the most used anti-hypertensive agents in humans. These drugs known for their ability to reduce blood pressure in hypertension and improve the cardiovascular function in heart failure, among others. However, these agents are also associated with important adverse effects, such deleterious/dangerous reduction in Na^+ and K^+ plasmatic levels. Thus, the development of new diuretic agents with reduced adverse effects is important to improve the output in several cardiovascular diseases.

Urginea maritima

The White Squill (Urginea maritima) belongs to family liliaceae, it has been used as a medicinal plant through centuries over the world, believed to have certain traditional actions. The Squill bulb used by herbalists traditionally for the treatment of cardiac failure, chronic bronchitis, rodenticides and asthma. Novel cardiac glycosides have recently been isolated from squill known as ufodienolides. The plant is rare in the Mediterranean coastal region. It is found in all

North African countries, in the Mediterranean region and the Canary Islands. The medicinal parts come from the bulbs of the white variety collected after flowering and the fresh, fleshy bulb scales of the white red varieties.

White squill contains, active constituents, several steroid glycosides (bufadienolides). Including scil-laren A (scillarenin + rhamnose + glucose), gluco scillaren A (scillaren A + glucose). proscillaridin A (scillarenin + rhamnose), scillaridin A, scilli-cyanoside, scilly glucoside, scilliphaeoside (12 B-hydroxy proscillaridin A), and glucoscilliphaeoside (12 B-hydroxyscillaren), the most important being scillaren A and proscillaridin A. Scillaren B has been used to describe a mixture of squill glycosides as opposed to pure scillaren A.Other constituents present in white squill include flavonoides (vitexin, isovitexin, orientin, isoorientin, scoparin, vicenin-2, quercetin, dihydroquercetin or taxifolin, dihydroquercetin-4-monoglucoside.), stig-masterol, scilliglaucosidin, and mucilage (gluco-galactans). Scillaren A and proscillaridin A. Scillaren B has been used to describe a mixture of squill glycosides as opposed to pure scillaren A.

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The action of the drug is that of a cardiac stimulant, with three important further properties all dependent on its irritant constituents. In small doses, that would not affect the heart, it is a gastro-intestinal, a bronchial and renal irritant.

The two later properties make it a powerful expectorant and a fairly active diuretic. The difference between its actions as an expecto-rant and a cardiac stimulant would seem to indicate its possession of two or more active principles, one specifically affecting the secretory mucous membranes, and the other the circulatory apparatus. Squill combined with Marrabium and Tussi-lago in bronchitis, with Ipecacuanha in whooping cough.

II. CONCLUSION

Traditional medicine known as indigenous or folk medicine comprises knowledge systems that developed over generations within various societies before the era of modern medicine.

The World Health Organization (WHO) defines traditional medicine as the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness. At the turn of the 20th century, folk medicine was viewed as a practice used by poverty-stricken communities and quacks.. The prevalence of folk medicine in certain areas of the world varies according to cultural norms. Some modern medicine based on plant phytochemicals that used in folk medicine.

The positive isotropic effect results mostly from blocking Na^+/ K^+- ATPase by glycoside constituent of the extract. The diuretic and natriuretic effects of the plant extract look like effects of potassium sparing diuretics. The hypertensive effect attributed to its diuretic property. The mechanism of bradycardia might be due to increased vagal tone, a reflex mechanism through baroreceptors.

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Role of Milrinone in Septic Myocardial Depression

Vinko Tomicic & Ivania Tomicic

INTRODUCTION

At present, myocardial depression (MD) in septic shock (SS) is more frequently recognized. In 1984, Parker et al. published 20 patients with SS where 50% of them showed a left ventricular ejection fraction (LVEF) less than 40%1. It was not until 2006 that it became more widely accepted that some degree of MD was present in this kind of patients2. However, the prevalence has been variable depending on the evaluation method, either through cardiac output (CO), measurement of troponins, B type Natriuretic Peptide or by echocardiography2-4.

In 2008 Vieillard-Baron et al. studied 67 patients with SS without a history of heart disease with transesophageal echocardiography. They estimated a mean incidence of MD greater than 60%, which manifests itself in the first 48 hours of evolution and recovers between seven and ten days after the onset of SS5.

Keywords: NA

Classification: NLM Code: WG 205

Language: English

Great Britain Journals Press

LJP Copyright ID: 392884

London Journal of Medical and Health Research

Volume 23 | Issue 4 | Compilation 1.0

Role of Milrinone in Septic Myocardial Depression

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I. INTRODUCTION

At present, myocardial depression (MD) in septic shock (SS) is more frequently recognized. In 1984, Parker et al. published 20 patients with SS where 50% of them showed a left ventricular ejection fraction (LVEF) less than 40%[1]. It was not until 2006 that it became more widely accepted that some degree of MD was present in this kind of patients[2]. However, the prevalence has been variable depending on the evaluation method, either through cardiac output (CO), measurement of troponins, B type Natriuretic Peptide or by echocardiography[2-4].

In 2008 Vieillard-Baron et al. studied 67 patients with SS without a history of heart disease with transesophageal echocardiography. They estimated a mean incidence of MD greater than 60%, which manifests itself in the first 48 hours of evolution and recovers between seven and ten days after the onset of SS[5].

Jardin et al. evaluated patients in SS echocardiographically and demonstrated to have normal end-diastolic volume but decreased stroke volume (SV), and those who survived developed more marked abnormalities in ventricular function at symptom onset, recovering LVEF once SS was overcome[6].

In 1985 the presence of a circulating myocardial depressant factor was confirmed by Parrillo et al. through the demonstration that the serum obtained during the acute phase of patients with SS was able to decrease the shortening rate of cardiomyocytes of rats in vitro, while the serum of patients non-septics restored its function[7]. Today it is known that interleukins 1 (IL-1), IL-2, IL-6 and TNF-α behave as circulating myocardial depressants factors[8].

There is also evidence of activation of apoptotic pathways that impair cardiomyocyte mitochondrial function. Likewise, there is adhesion of activated leukocytes to the cardiomyocyte via intercellular adhesion molecules that induce dysfunction and ultimately death of the cardiomyocyte[9,10].

On the other hand, the myofibrils show a decreased sensitivity to calcium, probably explained by I-troponin phosphorylation at the site where it combines with calcium[11]. In addition, it is recognized that MD is associated with increased intracellular nitric oxide (NO), which plays an indirect role through the formation of peroxynitrite, whose inhibition produces improvement in MD[12].

Given the above, it is postulated that MD could be explained both due to intra and extracardiac factors, ruling out the hypothesis associated exclusively with hypoperfusion, since that coronary blood flow in SS is preserved[13].

The use of inotropic agents in the management of the SS should induce improvement in left ventricular performance, increased mixed venous oxygen saturation/central venous oxygen saturation (SvO2/ScvO2) and reduction of serum lactate levels. Dobutamine (DBT) remains the drug recommended by the Surviving Sepsis Campaign to treat septic MD[14]. However, the β1-agonist agents may be less effective when there is down regulation of such receptors, oxidation of catecholamines by increased oxidative stress, and

inhibition of G protein associated with the β1-adrenergic receptor that prevents the activation of adenylate cyclase[15].

Tachyarrhythmias and increased myocardial O_2 consumption (VO_2), especially in patients in SS with low left ventricular filling pressures have been described[16]. On the other hand, Kumar et al. demonstrated that DBT increases LVEF more than 10% only in 35% of these patients[17].

Milrinone (MN), being an inhibitor of the phosphodiesterase III, exerts an inotropic effect increasing cAMP in the cytosol of the cardiomyocytes; however, due to its systemic vasodilatory effect it has not been widely recommended in septic MD[18,19].

Our group carried out a study where the impact of starting MN infusion in 72 patients with SS was evaluated. Pulse contour cardiac output (PiCCO system) to monitorizing the cardiovascular performance was used[20]. Improved in cardiac output (CO) and metabolic parameters (ScvO2, v-a CO2 difference, arterial lactic acid and base excess) were observed.

Table: Hemodynamic and metabolic parameters before and after start MN infusion

Parameters	Before MN	After MN	*p*
Cardiac Index	3.1 ± 1.0	3.3 ± 1.1	0.003
v-a CO2 difference	7.6 ± 3.3	6.0 ± 3.6	0.03
Lactic acid	18.75 ± 14.87	13.1 ± 9.1	0.01
ScvO2	71.1 ± 10.3	76.1 ± 7.3	0.004
Urine output	1070 ± 946	1490 ± 1243	0.0003
SVR	1931 ± 999	1753 ± 917	0.13
ITBVI [NV: 850-1000]	865 ± 181	902 ± 237	0.23

Table: MN: milrinone; $ScvO_2$: central venous oxygen saturation; SVR: systemic vascular resistance; ITBVI: intrathoracic blood volumen Index (PiCCO system), NV: normal value; values are expressed as mean ± standard deviation.

It is worth mentioning that the increase in CO was not due to a reduction in systemic vascular resistance (SVR) or improvement in preload (intrathoracic blood volume [ITBV]), which supports that the optimization of CO most likely it was due to an improvement in myocardial contractility. All events previously described occurred in absentia of hypotension and without the need to withdraw the infusion of MN[20]. Table

Liet et al., randomly studied injection-induced septic shock with pseudomonas in rabbits. One group received MN and the other placebo. MAP and cardiac index (CI) were measured every 30 minutes (PiCCO system) demonstrating a progressive fall of CI in the group without MN. No fall of MAP in the treated group was observed [21].

There are doubts regarding the additive effect of MN and DBT. Sakai et al., in rats with sepsis induced by cecal ligation and puncture (CLP) and a control group, demonstrating that the levels of cAMP were significantly elevated in both groups in response to MN, but with DBT only occurred in the control group (operated without cecal ligation and puncture)[22].

This phenomenon is attributed to the fact that the effect of DBT is affected in CLP rats because of cAMP phosphate hydrolysis due to up-regulation of phosphodiesterase IV (PDE-IV), without observing changes in the activity of ß1 receptors[22].

Wang et al, studied three groups of patients with SS: standard care, milrinone, and group

esmolol-milrinone. The benefits observed with the association of esmolol-MN are attributed to the reduction of heart rate and the release of catecholamines induced by esmolol, which optimizes the left ventricular end diastolic volume. Surprisingly, the group MN plus esmolol improved 28 days survival[23].

Schmittinger et al. analyzed 40 patients with SS and MD without previous heart disease, using MN plus enteral Metoprolol and concluded that this combination is viable in these patients[24].

In SS, regulation of vasomotor tone is due to the synthesis of vasoconstrictor and vasodilators molecules. The main vasodilator is nitric oxide (NO) whose production is increased by the greater expression of oxide inducible nitric synthase (i-NOS)[25]. In this vasodilation stage it is difficult to introduce inodilating agents that decrease vasomotor tone such as DBT (β2 effect) and MN[26].

Although MN causes more hypotension and reduced SVR than DBT, our results suggest that MN, as an isolated inotrope, could benefit patients with SS who are euvolemic and supported by noradrenaline (NAD)[20].

About 38% of patients with SS develop early septic MD (primary hypokinesia) and 21% will develop it in the next 24 to 48 hours, probably due to the increase in afterload induced by NAD (secondary hypokinesia). Consequently, the use of inotropic agents, by improving the contractility, may maintain or increase systemic blood pressure[4].

Therefore, dobutamine and MN can trigger arrhythmias due to intracellular calcium overload and myocardial ischemia secondary to imbalance between delivery and VO_2. Its use is also associated with increased mortality, emphasizing the importance of limiting the use, especially if they are administered in a combined manner[27].

Despite these disadvantages, many patients are unable to restore their organ functions without inotropic support.

In our study, the patients who used NAD and MN, 17.2% developed atrial fibrillation (AF), while in the group that used DBT+MN+NAD a 26.6% developed AF, without reaching significant differences[20].

If we compare DBT with MN, the first one produces greater stimulation of myocardial contractility, while MN produces greater vasodilation and reduction of left ventricular filling pressures.[28]

In addition, MN reduces pulmonary vascular resistance (PVR) more significantly than DBT, showing advantages in right ventricular dysfunction, such as in cases of pulmonary SS (primary Acute Respiratory Distress Syndrome) that evolve with elevated PVR due to hypoxic pulmonary vasoconstriction.

The association of MN to conventional treatment with DBT, dopamine and/or nitroprusside has been shown to have additive effects, improving ventricular ejection parameters. Colucci et. al, using intracoronary infusion of MN to avoid the peripheral effects of the drug, demonstrated an improvement in contractility in patients who were receiving dobutamine simultaneously, through a significant increase in dP/dt (coefficient between delta pressure and delta time of the arterial curve) with the combination of both drugs[29].

Meissner, studied the hemodynamic effects of DBT and MN administered in isolation and in combination, noticing that the combined administration produced more SV increase[30].

Poelaert et. al, with echocardiogram in 25 patients with SS identified 3 subgroups: (1) with preserved systolic function, (2) with diastolic dysfunction and (3) global failure[31].

Levosimendan favors the rate of diastolic relaxation (lusitropic effect) and MN by reducing the cAMP degradation also benefits ventricular filling, effect that is not observed with the β adrenergics agents[32,33]. Notwithstanding the foregoing, levosimendan is not superior to dobutamine as inotropic drug in SS[34,36].

In summary, a significant percentage of patients with SS evolved with MD. These patients required the inclusion of inotropes agents such as DBT and/or milrinone and in case of refractory

hypotension, they required epinephrine[37]. In our study it was observed that MN is a safe alternative as an adjuvant to treat SS with MD in patients who are adequately resuscitated (ITBV index: normal values: 850-1000 ml/min/M^2).

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