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STUDY OF PHYTOCHEMICAL, ANTIOXIDANT AND ANTI-INFLAMMATORY OF *MANGOSTEEN* (*G. MANGOSTANA*) AND ITS ABILITY TO WOUND HEALING

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Abstract

In this work, the study of *G. mangostana* properties was done by studying phytochemical screening, trace element and antioxidant activity. The study of fruit peel extract contents gave many compounds, the test of antibacterial done by using well diffusion method and the extract was tested on *E.coli and Staphylococcus aureus* bacteria. The toxicity of the peel extract was examined by giving the dose 50mg\b.w orally to laboratory animal (mice). The diagnosis of the result of pathological changes showed that extracts has no toxicity. After that, the peel extract was turn in to a cream and use as a wound healing cream. The result showed that the cream has higher activity as a wound healing than the extract only. The final results appeared that extract had a good bioactive compounds and antioxidant components, with the acceptable role in wound healing, which can be applied as good agents for antibacterial applications, Anti-inflammatory and it could be helpful for the preparation of pharmacologically useful drugs.

Key words: *G.* , Antioxidant, $LD_{50,}$ Anti-bacterial, Anti-inflammatory, wound healing

Introduction

García (G.) *Lin* is classified within *Guttiferae* family, has many medical properties like antibacterial, antifungal, antioxidant, anti-inflammatory, antitumor, cosmetic uses, so it is used in medicinal and pharmacological field. It is a tree with 7-8m high, known only from cultivation in South East Asia (Ibrahim *et al.,* 2016). Moreover, *G. mangosteen* has been shown to contain various secondary metabolites (e.g., prenylated and oxygenated xanthones) (Narasimhan *et al.* 2017). The peel of the fruit contains large amounts of phenolic antioxidants, such as terpenes, anthocyanins, tannins, flavonoids and polyphenols (Tachaprutinun *et al*. 2014). The free radicals like hydroxyl and superoxide radicals, which are known as reactive oxygen species (ROS). The aggregation of ROS can lead to oxidative stress (Li, *et al*. 2017). The antioxidants decrease the level of free radicals in the tissue by their self-repairing mechanisms in the cell (Li, *et al.* 2017). A wound can be defined as a disruption of cellular and anatomic continuity of a tissue with or without microbial infection. Disruption of epithelial tissue of the skin with the distraction of functional continuity of living tissue occurs in wound due to physical, chemical, thermal, immunological, and microbial exploitation (Lazarus *et al.* 1994). Inflammation is a complex biological response from vasculartissue to harmful stimuli, pathogens, irritating from redness, warmth, swelling and pain (Palladino *et al.* 2003). The wound healing process consists of four stages: hemostasis, sore, proliferation, cell migration, tissue reformation or dissolution. (Freiesleben *et al.* 2017). Medicinal plants have been shown to possess wound healing activity in animal studies through the highly content of active compounds (Mahmood *et al.* 2014). Here, we demonstrate the phytochemical contents, trace elements, antioxidant activity, antibacterial activity, study the toxicity of fruit on animal models and using of this extract as a wound healing agent.

Materials and Methods

Preparation of Aqueous *G.* fruit peel extract

The *G.* fruits were collected from local market. The

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peels were washed thoroughly with distilled water before being dried. The freshly cleaned peels were left to dry for 15 days at room temperature. All the peels were ground into fine powder using an electric blender and stored at room temperature for further used. The extract was prepared by taking 2.50 g of the powder with 100 mL distilled water and boiled at 60^0C for two Hours. The crude extract was filtered by using filter paper and kept in test tube at 4-5^0C for further used (Xin Lee *et al.* 2016).

2. Qualitative phytochemical analysis

According to the standard AOAC (1990) method (Chemists and Horwitz 1990). The chemical components of *G.* peel extract were detected by using different ways as shown in Table.1. They included (glycosides, alkaloids, saponins, phenolic compounds, tannins, flavonoids, steroids).

Determination of trace element and Nutritional content of *G.* peel extract

Ten ml of fruit peel extract of *G.* were placed in the centrifuge at 3500 rpm after that the liquid was separated from the precipitate by the filter paper and repeated the process for several times until a clear liquid was obtained. The trace elements were specified by (Shimadzu AA-670, Flame Atomic Absorption Spectrophotometer). The fruit of *G.* was sent to the Nutrition Research Institute in Baghdad to analyzing the fruit components (Mohammed and Abbas 2016).

FTIR Analysis

The peels' powder of *G.* was washed with distilled water several times to get rid of dust and dry it with 40 ºC in the oven. For comparison, the dried peels' powder of *G.* was analyzed by FTIR (shimadzu-8400S spectrophotometer), the spectrum was recorded in the range of 500-4000 cm^{-1} (Al-Alwani *et al.* 2015).

Qualitative determination of free radical scavenging activity (TLC method)

The antioxidant activity was analyzed by Thin Layer Chromatography (TLC) followed by DPPH (2, 2-Dipheny l-1-picrylhydrazyl). About 100 µg of *G.* peel extract and standard solution (gallic acid) were placed on TLC plates (Merck, 10 × 10 cm^2). TLC plates were air dried and observed under UV light (240 & 300 nm). Different separated points were established as their Rf values. After this assay, 0.05% of DPPH solution in methanol was sprayed on the face of TLC plates and incubated for 30 minutes in a dark place at room temperature. Active antioxidant *G.* and gallic acid appear as yellow spots against purple background (Cuendet *et al.* 1997).

Quantitative determination of Free radical scavenging activity assay (DPPH method)

The scavenging activity of *G.* peel extract was examined *in vitro* using DPPH radical as described by Shimada *et al*. (Shimada *et al.,* 1992), with slight modification. One ml of various concentrations (10-60 µg/ml) of extract was mixed with 0.5 ml of DPPH solution (1.3 mg DPPH/ml methanol) and the volume were made to 3 ml with methanol. The control prepared by adding 1.5 ml of DPPH (1.3 mg DPPH/ml methanol) with 1.5 ml methanol. Mixture were shaken vigorously and left to stand for 30 min in dark place and the absorbance were measured at 517 nm against a reagent blank (3 ml methanol). Gallic acid was used as standard. The sample quantity needed to reduce the initial DPPH concentration by 50% indicated to the IC50, which calculated graphically according to the equation

DPPH scavenging activity % = [1 – (A test sample or standard/ A control)] x 100

Where:

A control = Absorbance of DPPH alone

A sample = Absorbance of DPPH along with different concentrations of extract or standards

Antibacterial activity by well diffusion method

The *G.* peel extract was tested for its antimicrobial activity by well diffusion method against pathogenic organisms, *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*). Using micropipette, the samples (S7= Ethanolic peel extract 2.5g /25ml, S8=*G.* peel extract 2.5 g/25 ml) respectively, were prepared by serial dilution from the stock solution with deionized water and poured into wells on all plates. After incubation, the diverse levels of zone of inhibition were measured by millimeter (Chakraborthy *et al.* 2008).

LD_{50} analysis

In this study, we recorded the clinical signs of ten adult albino mice (male) for 24hrs till 14 days. They were divided randomly into two groups containing five mice (25-30g) for each group, all cured groups treated orally by gastric Gavage once daily with different doses of *G.* peel extracts following:

First: control group given distilled water.

Second: given *G.* peel extract at dose 50 mg/kg b.w orally by gastric lavage one time.

The mice were kept under continued observation for 24 hrs after the administration; at the end of LD_{50} analysis all the mice were sacrificed and vital organ (liver and brain) used for histopathological analysis (Soufane *et al.* 2017).

Histological Study

All mice were sacrificed after 24 hours of last treatment. The vital organ (liver and brain) were dissected out and keep in tube contain formalin 10% until sent for histological examination. The vital organ (Liver and brain) were dehydrated in progressively more concentrated alcohols, then embedded in paraffin and cut into sections of 4-5 µm thickness and stained with hematoxylin and eosin (H&E) for microscopical examination. The slides were examined using an optical microscope (40 × magnification) (Taddei *et al.* 2017).

Wound healing for mice

After the animals were anaesthetized dorsal fur was shaved and a full thickness of the excision wound of 0.5 cm^2 was created along the markings using a surgical blade and pointed scissors. The entire wound was left open until redness is indicative of acute inflammation. The wound closure rate was assessed by tracking the wound in days of all days until healed. The mice were treating on a daily basis and the observations that occur during the treatment process were record and changes in behavior that the animal exhibits were monitored during it (Prakashbabu *et al.* 2017).

Results and Discussion

Qualitative phytochemical analysis

The results indicate the presence of different phytochemical components (Table 1) in the *G.* peel extract such as Glycosides, phenolic compounds, Tannins, resins, flavonoids, alkaloids, terpenoids and not containing steroid. Our results inagreed with the study of Obolskly *et al*., (2009).

Table 1: Qualitative phytochemical analysis of *G.* fruit peel extract.

Components	Reagents	Note	Result
Glycosides	Iodine test Molish test Benedict test	..... Purple ring Blue solution	-ve +ve +ve
Phenolic compounds	Ferric chloride $FeCl_3$ 3%	Green ppt	+ve
Tannins	Ferric chloride $FeCl_3$ 3% Lead acetate 0.1 %	Green ppt Yellow ppt	+ve +ve
Resins	Ethanol	Turbidity	+ve
Flavonoids	Ethanol + KOH	Yellow ppt	+ve
Alkaloids	Mayer's reagent Wagner reagent Picric acid	White ppt Brown ppt Yellow ppt	+ve +ve +ve
Terpenoids	$CHCl_3 + H_2SO_4$	Reddish brown	+ve
Steroids	Ethanol + acetic anhydride + H_2SO_4	Blue/green	-ve

Table 2 : Trace elements in *G.* fruit peel.

Trace elements in *G.* fruit peel	
Element	**Concentration (ppm)**
Se	3.944
Fe	0.232
Cd	0.011
Co	0.0069
Zn	76
Cu	20
Mg	10
Ca	8
Pb	6
Mn	0.021

Table 3 : Nutritional content in *G.* fruit peel.

Nutritional content in *G.* fruit peel	
Composition (g/100g)	**Percentage %**
Moisture	20%
Protein	2.05%
Fat	1.38%
Ash	3.754%
Fiber	4.60%
C.H.O	68.54%

The trace elements and Nutritional content of *G.* fruit peel

The trace elements found in *G.* fruit peel were Cadmium, Iron, Selenium, Cobalt, Zinc, Copper, Magnesium, Calcium, Lead, Manganese and the Nutritional value per 100 g of fruit shown in Table 2, 3. Our results inagreed with the study of Susy Tjahjani, *et al.,* (2014).

We can note from the data that the plant rich in many substances, including proteins, fats, fiber and carbohydrates, which can be used in this study, including various antioxidants and trace elements that can be use in pharmaceutical, medical and other applications.

FTIR analysis

The FT-IR analysis was used to identify the possible bio-reducing molecules in *G.* peel. The spectra of the fruit peel have been shown in Fig. 1.

The FT-IR analysis of *G.* peel was used to identify the reactive groups could be found in phenols, ûavonoids and benzophenones. Aside O-H stretching, at the region of 2933 cm^{-1} and 3103 cm^{-}

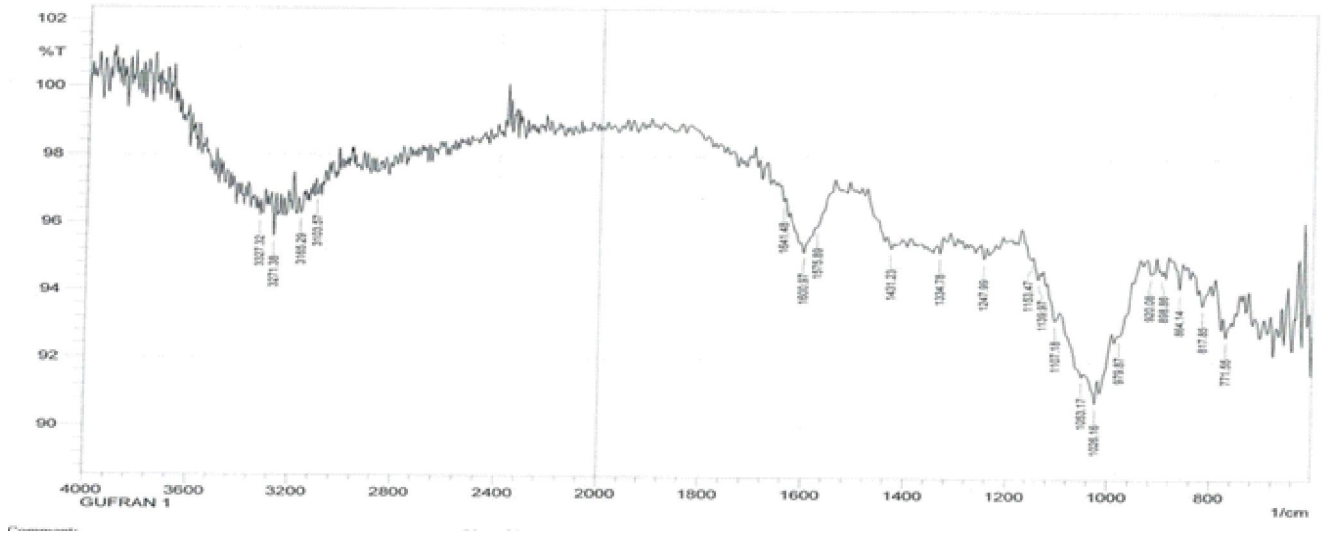


Fig. 1: FTIR spectrums of *G. fruit* peel.

[1] corresponds to the C-H bond in xanthone and other compounds had this bond. The two Bands, 3271 cm^{-1} and 3296cm^{-1} belong to C-H, while at the region of 1700 cm^{-1} it shown the presence of C=O group. At the region of 1600–1500cm^{-1}, C-C in ring aromatic bond also suggests the presence of aromatics structure exists in the *G.*. The C-C aromatics stretch was observed for both spectra at the region of 1500–1400 cm^{-1} which was relevant to the aromatic backbone that could be found mainly in the peel of *G.* . All the above results were matching to different components like phenols, ûavonoids, benzophenones and xanthone (Harrison 2002).

Qualitative and quantitative determination of free radical scavenging activity

The major mechanism of antioxidant action in foods is the radical scavenging activity. thus, many ways in which antioxidant activity has been evaluated by scavenging synthetic radical in polar organic solvents such as methanol (Choo and Yong 2011). In free radical scavenging activity, DPPH is one of the stable and commercially available organic nitrogen radical which has a UV–visible maximum absorption at 517 nm (Huang and Prior 2005). In our study, the antioxidant activities of fruits (peels extract of *G.*) were determined using free radical scavenging activity. The color changes from purple to yellow as the molar absorptivity of the DPPH radical at 517 nm reduce upon the transfer of acidic H-atom from the compound to DPPH radical to form DPPH-H. The resulting decolourization is stoichiometric with respect to number of electrons captured. The results are summarized in Fig. 2, Fig. 3, Fig. 4 and Table 3.

Radical-scavenging properties of gallic acid and *G.* peel extract were evaluated against the DPPH radical.

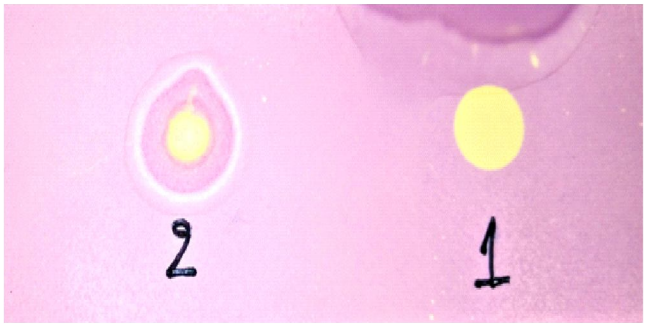


Fig. 2 : The TLC photo-image for (1) gallic acid (2) *G.* peel extract.

Table 4: The percentage inhibition of standard gallic acid and *G.* peel extract.

Concentrations (ig/ml)	% Inhibition (standard solution-gallic acid)	% Inhibition (G. peel extract)
10	43.98	42.7
15	46.01	45.2
25	83.4	48.6
50	60.6	51.8
60	82.9	52.5

By using DPPH as a TLC spray, gallic acid and *G.* peel extract appeared as yellow spots against a purple background. Our results show that it has a potent scavenging activity and IC_{50} and the scavenging activity for the fruit extract is (39 µg\ml).

Anti-bacterial studies

In the present study, two pathogenic bacteria (*E. coli* and *S. aureus)* were used in this test Their sensitivity was tested for different concentrations of *G.* peel extract by using well diffusion method (Fig. 5). The diameters of the inhibitory region are presented with each extract to the selected bacteria. All four extracts; ethanol extract

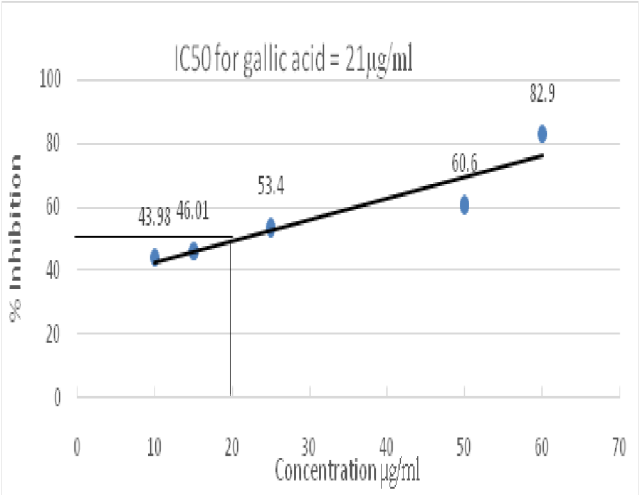


Fig. 3: DPPH free radical scavenging activity of standard solution (gallic acid).

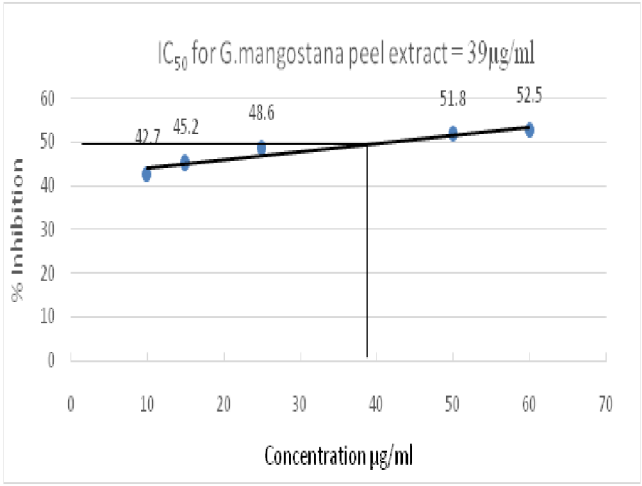


Fig. 4: DPPH free radical scavenging activity of *G.* peel extract.

of *G.* peel, aqueous extract of *G.* peel, which exhibited inhibitory regions of about 6-12 mm against some bacteria, suggesting a broad activity against both positive and negative gram negative bacteria (Rajakannu *et al.* 2015; Jebalsy *et al.* 2017).

The LD_{50} Examination and Histological Study

The toxicity examination of the *G.* peel extract compared with control group shows that after the plant was given to the laboratory animal, a many of clinical signs like tacky cardiac, slight shivering of whole body with stiff skin hair appears after few minutes of given extract, but after 24 hrs all signs disappeared and all animal get back to normal situation this might be due to the nature of the peel contents with active ingredients that shown their effects immediately after submitting. The peel extract has no mortality or morbidity, while appearance

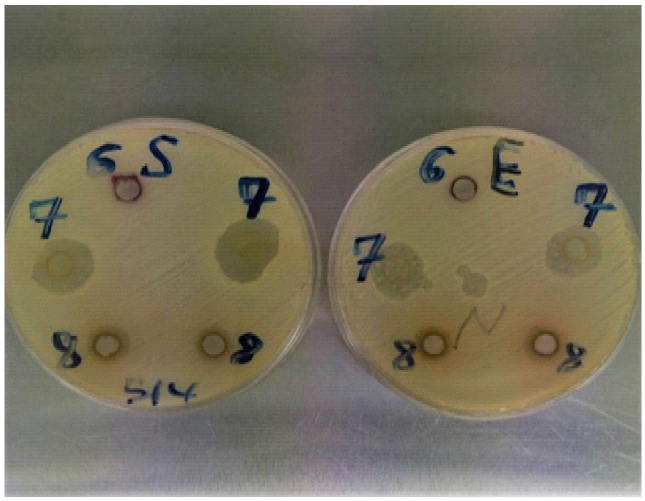


Fig. 5 : The inhibition zone for (7= Ethanol extract of *G.* peel, 8= Aqueous extract of *G.* peel, S=*S. aureus*, E= *E. coli*).

Table 5:The LD_{50} examination and sign of animal (mice) treated with *G.* peel extract.

Dose of extract	No. of mice per group	No. of dead/ No. of animal (mice)	Sign of animal treated with *G.* peel extract
50 mg/kg	5	0/5	Tacky cardiac, slight shivering of whole body with stiff skin hair appears after few minutes of given extract.

of different signs, revealed that the peel extract was not toxic with this dose or concentration used (Hsu *et al.,* 2011).

Histopathological study

The Histopathological observations show that Liver section of the group of mice treated with *G. mangostana* peel extract has Congestion, degenerative changes, depletion of glycoprotein (Fig. 6), while in Brain, the section of mice group treated with peel extract has normal structure appearance of glial cell with normal appearance of thyroid gland (Fig. 7, A and B) as compared with control (Fig. 8).

It is clear from the acute toxicity test of *G.* peel extract compared to control group, that the laboratory animal (mice) showed a number of clinical signs like irregular heartbeat, simple tremor, stiffness or hardening of hair which continue for a period of time from (1-2) hours, but after 24 hours, this clinical changes disappeared and the mice return to normal status. This may be due to the nature of the plant extract and its large quantity of active ingredients that show its effects immediately after the extract given but all sign disappeared within the continuous cellular metabolism [28]. Furthermore, the extract didn't

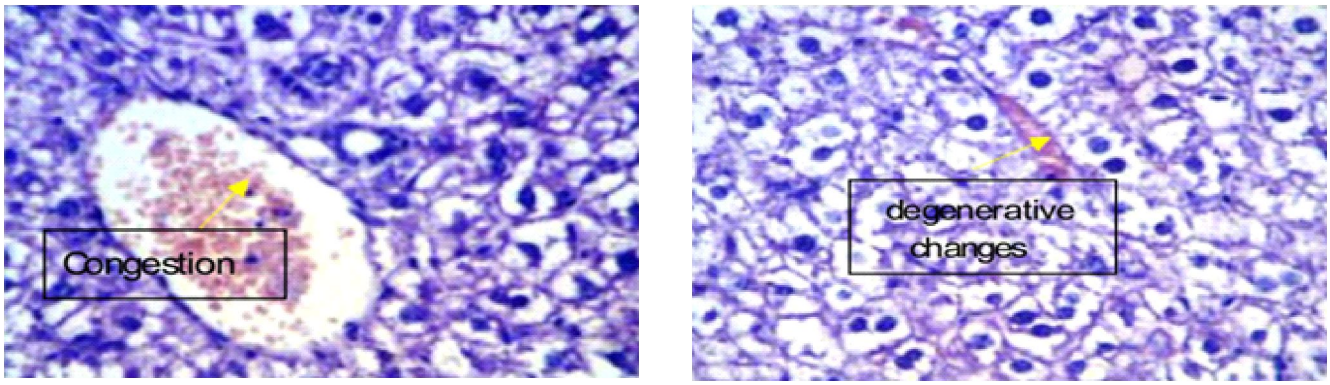


Fig. 6 : liver section of mice treated with *G.* peel extract (H&Ex400) congestion, degenerative changes and depletion of glycoprotein

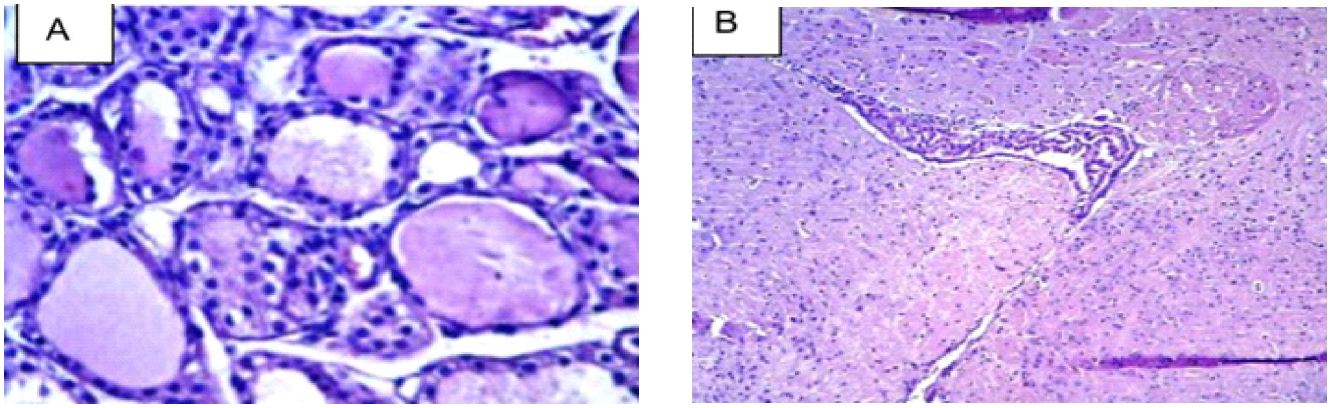


Fig. 7 : (A) Thyroid glandsection of mice treated with *G. mangostana* peel extract

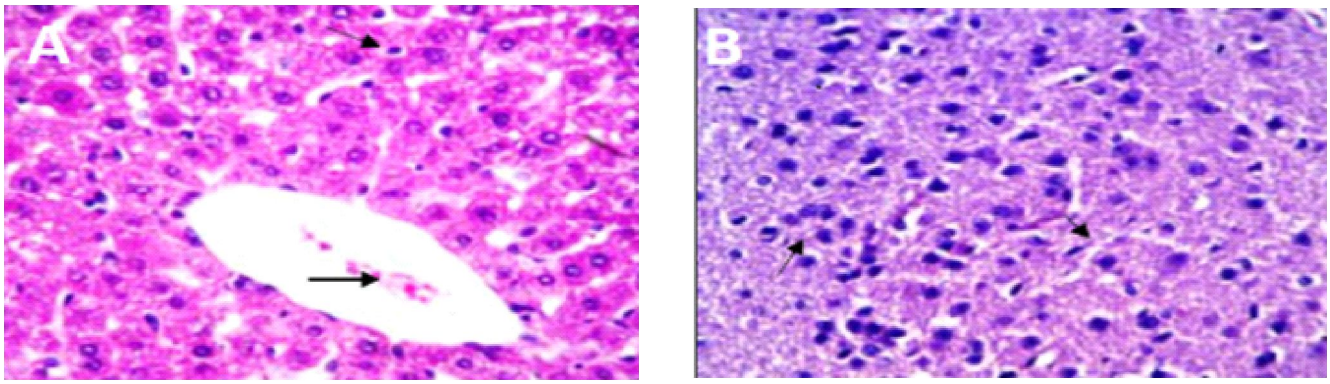
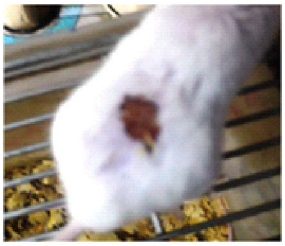
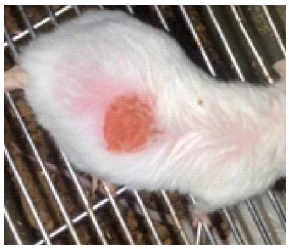
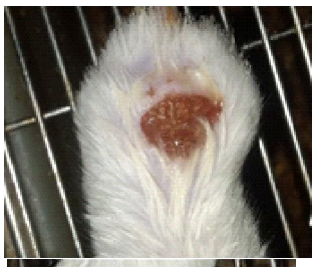
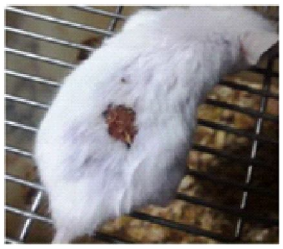
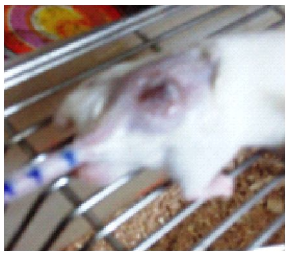
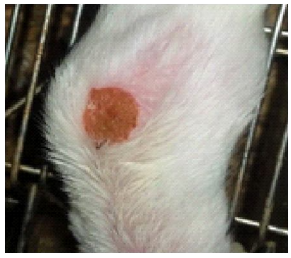
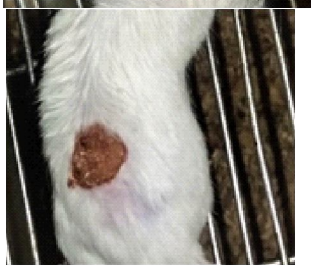
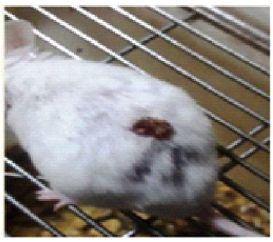
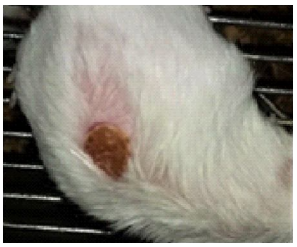
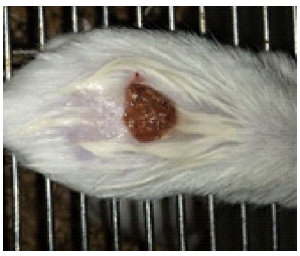
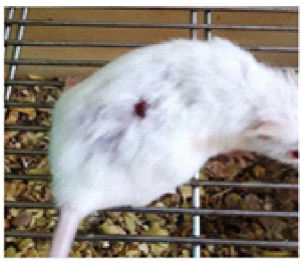
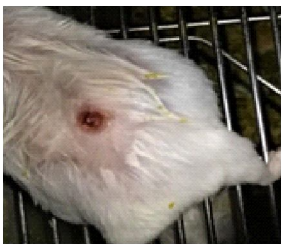
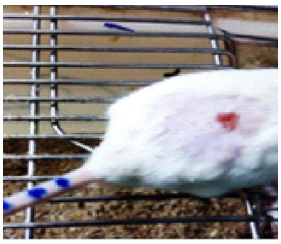
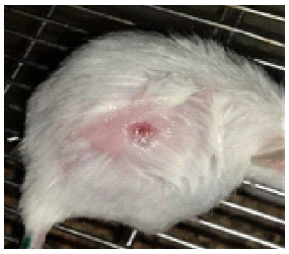
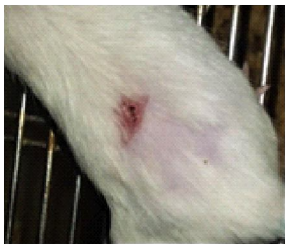


Fig. 8 : (A)Control Brain section of mice(H&Ex400):normal histological appearance ofglial cell, (B) Liver control (H&Ex400): the section reveal radial arrangement ofhepatocyte, sinusoid originates at lobules margin toward the hepatic vein (c.v.)

show any sign of mortality or morbidity in all mice treated with extract. Ourexperimental group different degrees of hepatic affection have been shown and this can be attributed to the oxidative stress caused by the extract (Lambert *et al.,* 2010). The liver section of mice group treated with *G.* peel extract show congestion of sinuses, central and portal veins and these lesions reflect the slight liver injury and the peel extract not toxic (Saleh *et al.,* 2013). Our explanation may be due to swollen of periportal cells that compress the adjacent sinus pressure and blood flow resistance within the sinuses, causing pressure on the portal vein (Serov, 1991). Lipid droplets considered as regulated organelles that acts as energy resources and fat storage compartments. Moreover, the accumulation of fat droplets in liver cells can be a compensatory mechanism whereby cells try to maintain some energy after mitochondrial destruction (Kühnlein, 2012). The results showed that the cells were rectangular with the deposition of glycoprotein in the vicinity. This result showed that after liver injury for any reason, the cells were transformed from an inactive state into activated cells producing extracellular matrix proteins,

Table 6: The effectiveness of the pharmaceutical formulation of *G.* peel cream at a concentration of 1 % w/w in wounds healing created on the skin of mice.

Days	Control group	Standard (Fucidin) group	Cream of*G.* peel extract (1% w/w) group	Treated with *G.* peel extract
1				
3				
6				
9				
12				

such as proteoglycans and collagen (Fausther *et al.*, 2013).

Treatment of developed wounds (wounds healing)

The ointment was used in treatment of mice wound. The ability of this ointment to made the wound healing developed faster than the aqueous peel extract as seen in the figures, where the ointment speeds up the process of the formation of scartissue in the outer skin areas. One of the explanations is the active substances found in *G.* peel extract that interact with the components of ointment, giving ointment more effective therapeutic role, ointment works on The formation of the outer cover surrounds the open wound completely, so that it can be avoided it from external influences, as well as the ability of the ointment to penetrates into the skin tissue which

increases the tensile strength in the skin tissue and increases the height of the production of the epithelial layer and collagen formation around the wound area, thus enhance the healing process and return the mouse skin to it is normal state. Furthermore, no side effects or changes in mice behavioral were observed with long treatment period (Tahir *et al.,* (2017).

Conclusion

This work presented evidence showing the phytochemical, trace elements and antibacterial activity of Mangosteen (*G. mangostana*) fruit peel, as well as, the fruit peel was a good source for antioxidant components, which observed by DPPH method. The histological study indicated that peel extract had no toxic effect. Also, it had ability to wound healing by using the peel extract as acream, which showed an amazing ability to healing wounds and had a higher activity than the aqueous extract alone. This may be useful in different applications in biomedical, pharmaceutical fields and industrial appliances.

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