Comparison the protective effect of bee honey alone or combined with its different products against some effects of paracetamol overdose in rats

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Abstract:

Paracetamol is a wide analgesic drug used without prescription especially after the COVID-19 pandemic without attention to its potential side effects and toxicities risks. Paracetamol overdose can cause oxidative organs injury mainly liver and kidney being the most difficult medical conditions increasing through the years especially in Egypt. Although bee products prolonged used as medicine in ancient Egypt due to their well-known health properties, there are a limited studies on clover honey. So, this study compared the protective effects of Egyptian clover honey, a cheap and popular type, alone or enhanced with 3% different bee products (propolis, pollen, royal jelly and their equal mix) (5g/kg b.w.) vs. silymarin (50 mg/kg b.w.) as antioxidant drug against some toxic effects of paracetamol overdose (650 mg/kg b.w.) in rats for 2 weeks. Also, honey chemical composition, total phenols and flavonoids and antioxidant activity plus sensory evaluation of jams made of honeys were done. Adding different bee products to honey enlargement its total phenols, antioxidant activity and nutritional profile as raises protein, ash, fat and fiber while carbohydrates were reduced. Enhanced honey with different bee products attenuated paracetamol oxidative and inflammation effects as nitric oxide and malondialdehyde reduction plus total antioxidant increase leading to reno-hepatoprotective with best effect for honey plus pollen and mix, while honey with royal jelly was the strongest uric acid lowering effect. Also, improvements in lipids profile and atherogenic indices were detected by best effects for honey with propolis and mix. Honey group results reached to healthy group and silymarin drug which is sometimes more effective. Additionally, jams sensory evaluation made of honey showed good acceptability, keeping its texture

without smoothing the surface or saccharification indicating good technological properties than sucrose jam, plus lovely flavor of honey with pollen jam which is near to clove. Although enhanced honey can be used as it is or even added to the water for health purposes but including it within different foods enhances their consumption. These findings highlight the detoxified effects of supported Egyptian clover honey with different bee products against paracetamol toxicity which still need more specific searches to prove and detect the perfect type of honey and bee products, effective safe dose, form, and period toward these respects considering the variation in bioactive components and their mechanisms, plus new technological food applications.

Key Words: Acetaminophen, painkillers, N-acetyl-p-aminophenol, hepatoprotective and reno-protective.

مقارنة التأثير الوقائي لعسل النحل بمفرده أو مختلطا مع منتجاته المختلفة ضد بعض تأثيرات الجرعة الزائدة من الباراسيتامول في الفئران

المستخلص:

الباراسيتامول هو دواء مسكن واسع الانتشار يستخدم كثيرا بدون وصفة طبية خاصة بعد جائحة كوفيد-١٩ دون الاهتمام بآثاره الجانبية المحتملة ومخاطر السمية. يمكن أن تسبب جرعة زائدة من الباراسيتامول تلف تأكسدي لعديد من الأعضاء وخاصة الكبد والكلى وهي من أصعب الحالات الطبية المتزايدة على مر السنين خاصة في مصر. وقد تم استخدام منتجات النحل لفترة طويلة كدواء في مصر القديمة بسبب خصائصها الصحية العديدة المعروفة على الرغم من وجود عدد محدود من الدراسات حول عسل نوارة البرسيم. لذلك، قارنت هذه الدراسة التأثيرات الوقائية لعسل البرسيم المصري، وهو نوع عسل رخيص ومنتشر على نطاق واسع، بمفرده أو معززًا بنسبة ٣٪ من منتجات النحل المختلفة (البروبوليس وحبوب اللقاح وغذاء ملكات النحل ومزيج متساوٍ منها) (بمقدار ٥ جم / كجم من وزن الجسم) مقابل السليمارين (٥٠ مجم / كجم من وزن الجسم) كدواء مضاد للأكسدة ضد بعض الآثار السامة لجرعة زائدة من الباراسيتامول (٦٥٠ مجم / كجم من وزن الجسم) في الفئران لمدة أسبوعين. كما تم إجراء التركيب الكيميائي للعسل، وإجمالي الفينولات والفلافونويدات، ونشاط مضادات الأكسدة، بالإضافة إلى التقييم الحسي للمربى المصنوعة من العسل. أدت إضافة منتجات النحل المختلفة إلى العسل إلى زيادة إجمالي

الفينولات، ونشاط مضادات الأكسدة، وقيمته الغذائية، حيث ارتفعت نسبة البروتين والرماد والدهون والألياف، بينما انخفضت نسبة الكربوهيدرات. أدى تعزيز العسل بمنتجات نحل مختلفة إلى تخفيف آثار الباراسيتامول المؤكسدة والالتهابية، حيث انخفض أكسيد النيتريك والمالونديالدهيد، بالإضافة إلى زيادة إجمالي مضادات الأكسدة، مما أدى إلى حماية الكلى والكبد، وكان أفضل تأثير للعسل مع حبوب اللقاح والخليط، بينما كان العسل مع غذاء ملكات النحل أقوى تأثير في خفض حمض اليوريك. كما تحسنت صورة الدهون ومؤشرات تصلب الشرايين وكانت أفضل النتائج للعسل مع البروبوليس والخليط. وصلت نتائج مجموعات العسل إلى المجموعة الصحية ودواء السليمارين، والتي كانت في بعض الأحيان أكثر فعالية. بالإضافة إلى ذلك، أظهر التقييم الحسي لمربى العسل قبولاً جيداً، مع الحفاظ على قوامه دون تجلد أو تسكر، مما يدل على جودة خصائصه التكنولوجية مقارنة بالسكروز، بالإضافة إلى نكهة العسل اللذيذة مع مربى حبوب اللقاح التي تقترب من نكهة القرنفل. على الرغم من أنه يمكن استخدام العسل المعزز كما هو أو حتى بإضافته إلى الماء لأغراض صحية، إلا أن إضافته إلى الأطعمة المختلفة يحفز استهلاكه. تُبرز هذه النتائج التأثيرات المُزيلة للسموم لعسل البرسيم المصري المدعوم بمنتجات النحل المختلفة ضد سمية الباراسيتامول، والتي لا تزال بحاجة إلى مزيد من البحوث المتخصصة لإثبات وتحديد النوع المثالي من العسل ومنتجات النحل، والجرعة الآمنة الفعالة، والشكل، والفترة الزمنية في هذا الصدد، مع الأخذ في الاعتبار تباين المكونات النشطة بيولوجيًا وآلياتها، بالإضافة إلى التطبيقات الغذائية التكنولوجية الجديدة.

الكلمات المفتاحية: أسيتامينوفين ، ن– أسيتيل– بارا– أمينوفينول ، وقاية الكبد ، وقاية الكلي ، المسكنات.

Introduction

Acetaminophen, which is known as paracetamol (PCM) or N-acetyl-p-aminophenol (APAP), is considered one of the most popular used medications worldwide as analgesic and antipyretic drugs without prescription in many countries (**Sarkar et al., 2022; Aboshama et al., 2024; Jaeschke and Ramachandran, 2024).** Paracetamol has elevated its use because of the COVID-19 pandemic without attention to its potential side effects and toxicities risk (**Madariaga-Segovia et al., 2023)**. A survey study on 176 Egyptians by **Mostafa et al. (2022)** showed

that 24.4% knew a lot about paracetamol and its possible toxicities while among participants, 62.5% thought paracetamol was safer than other drugs with similar purposes and 42.6% were able to recommend non-prescription paracetamol to others. Paracetamol overdose is common around the globe which attributed to its presence in many combination medications (**Jaeschke and Ramachandran, 2024**), long treatment periods even in a nontoxic dose (**Aboshama et al., 2024**), and/ or higher doses that more than 4g/day in adults (**Sarkar et al., 2022; Attaullah et al., 2023**) and which for someone at levels only just above the recommended dose (**Burns et al., 2018**) regardless of its therapeutic benefits and general safety at the recommended dose (**Sarkar et al., 2022; Attaullah et al., 2023; Aboshama et al., 2024**). Paracetamol toxicity is related to the dose which is nontoxic if it remains less than 75 mg/kg whereas if it increases more than 150 mg/kg, the overdose could be serious (**Dear, 2024**). By paracetamol overuse, hepatotoxicity and/ or nephrotoxicity plus brain toxicity can be developed via oxidative injury mechanism **(Yousef et al., 2010; Aboshama et al., 2024; Dear, 2024)**. Approximately 100,000 persons in the United Kingdom visit hospitals each year following a paracetamol overdose (**Dear, 2024**). One out of every 500 overdoses of paracetamol in England, develop liver failure (**Public Health England, 2017**). More than 50% of paracetamol overdoses are linked to liver failure and around 20% of liver transplantation in the United States (**Yoon et al., 2016**). **Hegazy et al., (2021)** revealed that drug overdoses are the leading reason for acute hepatic failure in both the United Kingdom and the United States as well as in Egypt. Between 1990 and 2017, there was a 74.5% increase in the cirrhosis prevalent cases number as an increase in ASR (age-standardized rate) by 0.75% per year and Egypt had the highest ASR (**Younossi et al., 2023**); liver illnesses are one of the most difficult medical conditions in the world and its incidence rate has been rising dramatically through the years by different etiological evolutions (**Jaafar et al., 2021)**. Also, CKD (chronic kidney disease) is a serious global health problem contributing to several comorbidities and death being around 9.1 to 13.4% (700 - over 800 million) worldwide and 7.1 million as 10.6% in Egypt in 2017, And the number is expected to double by 2030 (**Gawad et al., 2024)**.

Under this status, many compounds have been tested globally for their ability to inhibit paracetamol toxicity, and those with antioxidant activities were of special interest; since antioxidants are crucial in the regulation of a wide range of pathological and physiological processes contributing to tissue and cell protection from deleterious actions of reactive oxygen species (ROS) and other free radicals plus they enhance the immune system, modify harmful metabolism, alter cell proliferation and stimulate the DNA repair of damage **(Yousef et al., 2010; Naggayi et al., 2015**). Natural products or their derivatives may be a suitable option as organs protective agents **(Islam et al., 2021; Attaullah et al., 2023; Abduh et al., 2023)**.

Honey as a natural product and bee products (propolis, royal jelly, and pollen) have made the attention of researchers as supplemental and alternative therapies due to their well-known health properties as free radical scavenging, antioxidant and anti-inflammatory activities related to their phenolic substance (flavonoids and phenolic acids) content **(Nassar et al., 2020)**; which vary relating to the geographical location, floral origin, the season, the altitude, and types of honeybees **(Tavares et al., 2022; Abd El-Aziz et al., 2023)**. Honey is advised as a natural therapy either by itself or in combination with herbs in many traditional systems **(Kumar et al., 2024)**, since in ancient Egypt, China, and Greece, bee products have been utilized for centuries in medicine **(Denisow and Denisow-Pietrzyk 2016; Sultana et al., 2022)**. It is a naturally occurring, nutrient-dense, and antioxidant-rich food that is often utilized as a natural sweetener with no negative side effects **(Kumar et al., 2024)**. Clover honey is regarded as a premium bee product worldwide and in Egypt; and while research on the phytochemical profile of different kinds of honey and their related bioactivities continues to grow, there have only been a limited studies number on clover honey types to date **(Sultana et al., 2022)**.

So, this study aimed to compare the protective effects of enhanced Egyptian clover honey, a cheap and widely found honey type, with different bee products (propolis, pollen, royal jelly, and their equal mix) vs. silymarin as an antioxidant drug against some toxic effects of paracetamol overdose in rats.

Materials and methods

Materials

Bee products, and jam components:

Clover honey and other bee products (propolis, pollen, royal jelly) were obtained from Bee Products Research Unite of the Agriculture Faculty at Menoufia University in winter. Jams components of strawberry fruits, sugar, lemon, and vanilla were bought from the local market in Egypt, Menoufia, Shiben El-Kom.

Drugs:

Silymarin and paracetamol were purchased from a locally registered drug supplier, El-Ezaby pharmacy in Shebin El-Kom City, Menoufia Governorate, Egypt.

Experimental Animals and Ethical Approval

Forty-eight healthy adult male albino rats, weighing (150±10) g, were obtained from the National Research Institute, Animal House (Cairo, Egypt). Rats were kept in groups in well-ventilated cages under sanitary conditions in The Biological Laboratory, Home Economics Faculty, Nutrition, and Food Sci. Department, Shibin El-kom (Menoufia), Egypt, and consumed standard diet AIN-93 as reported by **Reeves et al. (1993)** for a seven-day adaption period while water and food were allowed ad libitum. This study was approved by the Institutional Animal Ethics Committee of Menoufia University (Reg. No, MUFHE /F/NFS/21/24).

Chemical kits

Biochemical assay kits were purchased from the Company of Biodiagnostic, El-Doky, Egypt.

Methods

Determination of main chemical composition, total phenolics, total flavonoids, and antioxidant activity

The main chemical composition of clover honey alone or mixed with 3% different bee products (propolis, pollen, royal jelly, or their equal mix) as moisture, ash, fiber, fat, and crude protein were measured according to the **AOAC (2012)** methods. Total carbs were determined using differences as follows:

% Carbs = 100 - (moisture%+% fiber+%Ash%+protein%+% fat).

Total phenolics were determined by the Folin–Ciocalteu (FC) reagent-based colorimetric test as showed by **Singleton and Rossi (1965)** which was given as mg/100g and estimated as gallic acid equivalent (GAE). Total flavonoids contents were determined utilizing the PH-differential technique explained by **Munhoz et al. (2014)**. Antioxidant activity was evaluated using the DPPH radical scavenging test **(Gülçin et al., 2010)**.

Experimental design

A total number of 48 mal albino rats weighted 150 ± 10 g could be used. All rats were fed on basal diet for 7 consecutive days to adjust, then rats were divided into 8 groups each of 6 rats as follows: group (1): negative control group; group (2): rats received paracetamol (650 mg/kg b.w.) orally intragastric once a day for 2 weeks as overdose control positive group, based on previous searches that used paracetamol at the same dose and duration **(Yousef et al., 2010; Islam et al., 2021; Attaullah et al., 2023; Abduh et al., 2023)**, Groups (3, 4, 5, 6, 7, and 8): rats orally received each of paracetamol (650 mg/kg b.w.) plus silymarin as an antioxidant drug at 50 mg/kg b.w. as previously used in **Islam et al. (2021)** and **Sarkar et al. (2022)** or clover bee honey alone or combined with 3% propolis, pollen, royal jelly, or an equal mix of them at 5 g/kg b.w. diluted in 2 ml of distilled water daily for 2 weeks respectively, based on the moderate honey dose used in previous searches as **Prakash et al. (2008)**.

Samples collection and biological evaluation

After the experimental period was complete, rats were weighed again, blood samples were collected from the aorta in dry, clean centrifuge tubes plus left to clot after fasting overnight and for 2 hours for water. The centrifuge for 15 minutes at 3000 rounds /min. to separate sera was used. The serum was stored in Eppendorf tubes at –20ºC until analysis **(Schemer, 1967)**. Also, the liver, kidney, and heart organs were dissected and weighed. The body weight gain (BWG%) and organ/ body weight were determined according to **Chapman et al. (1959)** using the following equations: BWG% = (Final weight – Initial weight) × 100 / Final weight; relative organs weight = organ weight × 100 / Final weight.

Biochemical assays

Oxidation status

Total antioxidant capacity (TAC), malondialdehyde (MDA), and Nitric oxide (NO) were determined according to **Alía et al. (2003), Eze et al. (2009),** and **Hu et al. (2009)** respectively.

Liver functions

The biochemical liver function markers including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl-transferase (GGT), and lactate dehydrogenase (LDH) levels were determined using the **Tietz et al. (1983), Henry (1974), Heersink et al. (1980) and Burtis et al. (2005)**. Also, the methods of **Varley et al. (1988), Spencer and Price (1977), and Srivastava et al. (2002)** in arrange were used to evaluate protein profile as total protein, albumin, and globulin, plus calculated albumin/globulin ratio (A/G ratio).

kidney functions

Serum creatinine, urea, uric acid, and were measured according to **Schirmeister (1964); Patton and Crouch (1977),** and **Fossati et al., (1980)** respectively.

lipid profile

The biochemical parameters of the lipids profile including triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL–C) levels were measured according to **Fossati and Prencipe (1982), Allain (1974), and Lopez (1977)** methods in order. While VLDL-c (very low-density lipoproteins) and LDL-c (low-density lipoproteins) were calculated according to **Friedwald *et al.*, (1972**) method as follows: VLDL-c (mg/dl) = TG/5 and LDL-c (mg/dl) = (Total cholesterol – (HDL-c +VLDL-c). The atherogenic index (AI), also known as the atherogenic coefficient (AC), was obtained by dividing non-HDL-C by HDL-C (AI = (TC - HDL C) / HDL C), as well as the atherogenic combined index (ACI), a novel lipid bioindicator, was calculated as following: ACI = (log 10 [Tri × "non-HDL-C÷HDL"] according to **Toprak et al., (2024)**.

Technological techniques

Preparation and Sensory evaluation of jam

Strawberry jams were made using the standardized method of **Awad and Shokry (2018)**, replacing sugar in control one with clover honey

alone or with 3% different bee products (propolis, pollen, royal jelly, or an equal mix of them) which were added at the end. Sensory evaluation for jam samples was done by 20 public members from Shiben El-Kom, City, Menoufia, Egypt. Panelists rated samples based on general acceptability as well as their taste, appearance, texture, color, and flavor (odder). A 1-10 rating system was employed, with 10 representing "great" and 1 signifying "dislike excessively. The Jame was assessed 6 hours after preparing in an open area at a normal temperature (25 °C) without additional lighting and water was available for rinsing. Statistics were used to evaluate precision and accuracy.

Statistical analysis

SPSS statistical program was used for data assessment. The findings were given as mean± SD, the statistics package program's one-way ANOVA testing was utilized to analyze the variances between groups, and Duncan's multiple comparison test was utilized as a post hoc test to evaluate the levels of significance at a significance level of $p \leq 0.05$ as the statistics package program **(Artimage and Berry, 1987)**

Results and Discussion

The main chemical composition, total phenols, total flavonoids, and Antioxidant activity of clover bee honey alone or combined with 3% of propolis, pollen, royal jelly, or their mix.

The main chemical composition, total phenols, total flavonoids, and Antioxidant activity of clover bee honey alone or combined with 3% of propolis, pollen, royal jelly, or their mix are shown in **Table (1).** Generally, it could be observed that adding different bee honey products as 3% of honey significantly raised the contents of protein, ash, fat, and fiber than bee honey alone except for the fiber content of honey plus royal Jelly (H-RJ) since the raised of it was non-significant. At the same time carbohydrate content was significantly reduced by adding different bee honey products compared to bee honey alone. These results indicate in general to enlargement of the nutritional value of bee honey by adding different products to it.

The highest value of protein content was recorded for honey plus pollen (H-Pol) and honey plus a mix of studied honey products (H-M) which didn't significantly differ from each other. The greatest values for

each ash, fiber in addition to fat were detected in honey plus 3% propolis (H-Pro) then honey plus 3% mix of the studied honey products (H-M). On the other hand, the least carbohydrate and fat contents were recorded in H-RJ which for carbohydrate content didn't significantly differ from each of H-Pol and H-M.

Table (1): The main chemical composition, total phenols, total flavonoids and Antioxidant activity of clover bee honey alone or combined with 3% of propolis, pollen, royal jelly or their mix.

Sample	Clover bee honey	honey+3% propolis	honey+3% pollen	honey+3% royal jelly	honey+3% mix
Chemical analysis (%)					
Moisture	17.84 ± 1.92^{d}	19.26c ± 0.47 ^{d}	20.84 ± 1.16 ^{bc}	25.11 ± 1.89 ^{a}	22.54 ± 1.46 ^{ab}
Protein	0.87 ± 0.16^{d}	1.78 ± 0.32 ^{c}	3.18 ± 0.22 ^{a}	2.21 ± 0.09 ^{b}	2.84 ± 0.16 ^{a}
Ash	0.23 ± 0.02^{e}	0.84 ± 0.06 ^{a}	0.41 ± 0.04 ^{d}	0.53 ± 0.04 ^{c}	0.70 ± 0.05 ^{b}
Fat	0.69± 0.05^{e}	1.56 ± 0.10 ^{a}	1.16 ± 0.08 ^{c}	0.98 ± 0.07^{d}	1.34 ± 0.06 ^{b}
Carbohydrates	80.36 ± 2.17^{a}	75.62 ± 1.29 ^{b}	74.15 ± 1.52 ^{bc}	71.11 ± 2.1^{c}	72.15 ± 1.76 ^{c}
Fiber	0.01 ± 0.002^{d}	0.94 ± 0.07 ^{a}	0.26 ± 0.02 ^{c}	0.06 ± 0.005 ^{d}	0.43 ± 0.03 ^{b}
Total phenol mg/g^{-1}	164.71 ± 9.79^{d}	246.84 ± 14.96 ^{a}	193.54 ± 8.46 ^{c}	187.24 ± 11.76 ^{c}	222.23 ± 12.77 ^{b}
Total flavonoids mg/g^{-1}	76.28 ± 6.52^{c}	98.16 $^{\pm}$ 4.84 ^{a}	85.45 ±5.55 ^{bc}	79.32 ± 2.68 ^{c}	91.76 ± 6.24 ^{ab}
Antioxidant activity (DPPH%)	67.16 ± 4.54^{b}	88.39 ± 5.49 ^{a}	86.11 ± 3.61 ^{a}	79.63 ± 5.53 ^{a}	85.74 ± 5.64 ^{a}

Data are expressed as mean ± standard deviation of three replicates. Values within a row having different super scripts are significantly different ($p \leq 0.05$) as indicate d by one-way ANOVA followed by Duncan's multiple range test (a > b > c > d > e > f).

It's important to notice that adding different bee honey products as 3% to honey significantly increased total phenols and antioxidant activity than honey alone. Although, the highest total phenols and flavonoids contents recorded for H-Pro and H-M, but the antioxidant activity (DPPH) significantly increased by adding different bee honey products as 3% to honey than honey alone and didn't significantly different from each other.

Bee honey and its products are a natural product made by honeybees that contain a variety of bioactive substances which linked to their preventive effects anti chronic diseases and their biological and therapeutic potential. There are several types of honey and its products from various parts of the world since the features and components of each type vary depending on floral origin, the geographical area and into the similar floral origin, the season, the altitude, and honeybee's species (**Tavares et al., 2022; Abd El-Aziz et al., 2023)**. Honey is an extremely concentrated complex mix of mainly 75–85% sugars, 13–20% water, and a small fraction of 3% of non-sugar constituents. The principal constituents of honey carbohydrates are about 33 to 38% fructose and 28 to 31% glucose, which represents 85–95% of total sugars **(Sultana et al., 2022; Badran et al. 2023)**. Other sugars involve disaccharides, such as sucrose, maltose, isomaltose, maltotriose, melezitose, melibiose, turanose, nigerose, and panose as well as 4 to 5% fructooligosaccharides, which can act as prebiotic agent **(Sultana et al., 2022)**. Honey's non-sugar components, although only found in comparatively small amounts, are thought to be crucial in determining not only its physicochemical and organoleptic properties but also its bioactivity profile **(Nguyen et al., 2019; Sultana et al., 2022)**. The honey mineral compounds concentration ranges from 0.1% to 1% **(Roby et al., 2020; Sultana et al., 2022)**. Potassium is the major metal, followed by calcium, phosphorus, sodium, magnesium, and sulfur while trace elements involve iron, zinc, copper, and manganese (**Sultana et al., 2022)**. Vitamins like C, B1, B2, B6, nicotinic acid, pantothenic acid (**Sultana et al., 2022)**, and vitamins A and E (**Abd El-Aziz et al., (2023**) are also found. Moreover, honey contains proteins in only minute quantities of 0.1–0.5% **(Roby et al., 2020; Sultana et al., 2022)**. Plant pollen, a natural contaminant present in honey due to bees' foraging activity, significantly contributes to the overall protein contents of honey, and a specific honey's protein amount also varies depending on the honeybee species that produce the honey and the presence of various bee enzymes. Honey also contains organic acids about 0.6% of honey and many enzymes (**Sultana et al., 2022)**.

Smetanska et al. (2021) revealed that the total phenolic contents of Egyptian clover honey (*T. alexandrinum L.),* varied from 18.574 mg to 53.314 mg gallic acid equivalents/g honey utilizing the Folin Ciocalteau

method, and the contents of total flavonoid determined to be 26.604 mg catechins/kg honey using a complex reaction by $AlCl_3$. Although **Roby et al. (2020)** reported a total phenolic content of 68.28 mg gallic acid equivalent to kg−1 fresh weight in Egyptian clover honey (*Trifolium hybridum*); and the honey antioxidant activity is fundamentally linked to the sample contents total phenols **(Roby et al., 2020; Sultana et al., 2022)** and determined to be 62.5 by using antiradical power method of DPPH **(Roby et al., 2020)**. Also, antioxidant activities were recorded at different levels for red clover honey **(Sultana et al., 2022)**. The suggested mechanisms involve the confiscation of free hydroxyl and superoxide radicals, hydrogen donation, and chelation of metallic ions **(Al-Mamary et al., 2002)**.

While research on the phytochemical profile of different kinds of honey and their related bioactivities continues to grow, there have only been a limited studies number on clover honey types to date (**Sultana et al., 2022)**. P-Coumaric acid noticed as the primary phenolic compound in ethanolic extract of Egyptian clover honey, donating about 83.0% **(Roby et al., 2020),** While gallic acid as 23.23 mg/100 g and (+)-catechin as 26.79 mg/100 g was found to existent by significant amounts between 15 phenolic components in Polish clover honey **(Jasicka-Misiak et al., 2017)**.

The existence of distinct phytoestrogenic isoflavonoids such as genistein, daidzein, formononetin, biochanin A, and glycitein within clover plant, and consequently, at clover honey should be furthermore researched to exploit novel opportunities of the potential benefits in both apiculture and pharmaceutical industries. The antioxidant activities of genistein plus other phytoestrogens have been established in various in-vitro or animal models (**Sultana et al., 2022)**. Moreover, royal jelly was reported to contain isoflavonoids like genistein, formononetin, and coumestrol **(Kumar et al., 2024)**.

Honey, propolis plus royal jelly, and bee pollen are the natural main source of chrysin, a flavonoid from flavone class members and has been reported to have many pharmacological properties as antioxidant, anti-inflammatory plus anti-apoptotic **(Mehrzadi et al., 2021, Kseibati et al., 2020 and Kumar et al., 2024)**. The pharmacologically active particles in propolis are flavonoids plus phenolic acids with their esters **Castaldo and**

Capasso (2002). Solorzano et al. (2024) and **Kumar et al. (2024)** ascribe propolis antioxidant capability to its substances of caffeic acid derivatives especially esters, the potential source for radical scavenging phytochemicals. Also, propolis is the natural resinous complexation mix produced via honeybees that contains bioactive components, as phenols (flavonoids plus phenolic acids), xanthones, and terpenoids; with the highest ingredients recognized in this product are 45 –55% balsams and resins, 5% fatty acids, 8 –35% waxes, 5 –10% aromatic compounds and essential oils, 5% pollen, and 5% mineral and organic compounds **(Tavares et al., 2022)**.

Royal jelly is recognized as an acidic secretion by a pH value of 3.5–4.2. It almost consists of 60–70% water; 7–18% sugars with fructose plus glucose considering the mainstream; 9–18% nutritionally valuable proteins (approx. 50% from the dry weight) which raise the Queen bee lifespan and consist of the peptides like royalisin, royalactina and jelleines plus trace amino acids relating with their biological and nutritional activity; 3–8% lipids in which main lipids consist of 10-hydroxy-2-decanoicacid (10H2DA) that known for its anti-cancerous and anti-angiogenic activity and sebacic acid (SA) that has anti-aging effects; about 1.5 % minerals with mineral salts and elements like Ca, P, Mg, S, Na, Cu, Zn, Fe, Cr, and Mn; plus vitamins B complex, C, A, and E, with a high level of B5 vitamin, related to lifespan extension. Royal jelly flavonoids are classified as flavanones (as hesperetin, isoakuranetin, and naringenin), flavonols (as kaempferol and isorhamnetin), flavones (as apigenin and glucoside of luteolin, chrysin, acacetin), and isoflavonoids (as genistein, formononetin and coumestrol). The numerous pharmacological aspects as antioxidant, inflammatory, and anti-apoptotic activities of royal jelly are contributed to its rich and unique components of proteins, lipids, carbohydrates, vitamins, minerals, polyphenols, and flavonoids along with many biological-active substances **(Kumar et al., 2024)**.

Bee pollen is considered a honeybee natural product promoted as valued source of energy and nourishing substances **(Denisow and Denisow-Pietrzyk, 2016)**, which parallels with the results of this study in which adding pollen to honey raises its content of the nutritional components, especially protein. It is loaded with proteins (5–60%),

especially free essential amino acids, also abound with reducing sugars (13–55%), lipid (4–7%) with bioactive substances like 1–10% unsaturated fatty acids (γ -linoleic, linoleic, and archaic) and 1.5% phospholipids, crude fiber (0.3–20%); in addition to contains minor components: minerals as Zn, Fe, Cu, Ca, Mg, with the high ratio of K/Na, vitamins as β-carotene (provitamin A), tocopherol (vitamin E), thiamine, niacin, folic acid, and biotin plus other vast range of plant secondary metabolites as pigments of organic carotenoid like lycopene and zeaxanthin, polyphenols with main flavonoids about 3–8% dry mass as chrysin, kaempferol, galangin, quercetin, isorhamnetin, catechins, and 1.1% phytosterols, terpenes, enzymes or co-enzymes and nucleic acids (especially RNA) **(Maruyama et al., 2010; Denisow and Denisow-Pietrzyk, 2016)**. Bee pollen has long been consumed as a complete, nutritionally balanced food in both Europe and the United States. **Maruyama et al. (2010)**. Because of its diverse composition and range of secondary metabolites, bee pollen is an extremely beneficial dietary supplement **(Denisow and Denisow-Pietrzyk, 2016)**.

These data parallel with the results of this study in which adding honeybee products such as propolis, royal jelly, pollen, or their mix to honey raises its nutritional profile, total phenols content, and antioxidant activity.

Protective effect of silymarin drug, clover bee honey alone and bee honey combined with 3% propolis, pollen, royal jelly, or their mix on serum total antioxidant capacity, lipid peroxidation as MDA and nitric oxide in rats received paracetamol overdose.

As shown in **Table (2)**, total antioxidant capacity (TAC) significantly decreased in rats received paracetamol overdose than control negative group. While malondialdehyde (MDA) as lipids peroxidation biomarker and nitric oxide (NO) as an oxidative stress and inflammatory agent were significantly increased by receiving paracetamol overdose at 650 mg/kg body weight for 2 weeks than normal rats. These results come in parallel with the findings of many searches that used paracetamol at various doses and duration as either a single acute toxic dose of 1 g/ kg b.wt. or a smaller toxic dose for periods starting by 3 days and ranging between 1 to 3 weeks or even a subtoxic dose for a prolonged period starting by 4 weeks. **Abdel-Zaher et al. (2007)** used paracetamol by both a single acute

toxic dose at 2.5 g/kg b.wt. and a smaller toxic dose of 750 mg/kg b.wt. for 1 week, also **Abduh et al. (2023)** used 600 mg/kg b.wt. for 3 weeks, **Aboshama et al. (2024)** used 500 mg/ kg b.wt. for different long durations as 4 weeks, while **Yousef et al. (2010)** and **Islam et al. (2021)** used paracetamol like that used in this study for 2 weeks as 650 mg/kg b.wt. and 640 mg/kg b.wt. and they found elevating each of NO levels in both serum **(Abdel-Zaher et al., 2007)** and hepatic tissue **(Abduh et al., 2023)** and MDA levels of liver, kidney, and brain **(Aboshama et al., 2024; Abduh et al., 2023; Islam et al., 2021)** plus decreasing antioxidant levels as decreases in GSH and antioxidant defense enzymes in serum and different organs intracellular for all doses and periods. The same results of oxidative status were shown by a single paracetamol dose of 600 mg/kg **(Raskovic et al., 2017)** and 200 mg/kg intraperitoneally for 2 weeks (**Neelima et al., 2020)**.

About 90% of paracetamol is converted in the liver to the non-toxic forms glucuronide and sulphate and removed via the kidney while small amounts 5–10% of the drug are oxidized by mixed-function oxidase enzymes (mainly cytochrome P450 system: CYP2E1, CYP1A2 and CYP 3A4) to the highly reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is rarely dangerous at recommended dosages because it attaches to glutathione (GSH) and is removed via bile, while overdosing of paracetamol leads to production excessive amounts of NAPQI which strongly react with liver GSH stores and deplete GSH rapidly and then combine with mitochondrial protein to generate paracetamol protein adducts resulting in intracellular dysfunction of mitochondrial and cellular death by oxidative stress since the generation of reactive oxygen species (ROS) and high reactive peroxynitrite via reaction between superoxide and nitric oxide increases in related to a marked GSH reduction levels in liver and or kidney intracellular **(Jaeschke and Ramachandran, 2024; Aboshama et al., 2024; Sarkar et al., 2022; Pingili et al., 2019; Abdel-Zaher et al., 2007)**. Moreover, it has been demonstrated that paracetamol high dose causes unsaturated fatty acids oxidation in the membrane of cells, which is related to lipid peroxidation and MDA rising level (**Islam et al., 2021).** This explains the results of increased NO plus MDA and lowered antioxidants.

In mammals, the family of nitric oxide synthase (NOS) from L-arginine involves three isoforms renowned as endothelial, neuronal, and inducible NOS and there are changes between them in which endothelial and neuronal NOS are constantly expressed and Ca^{+2} dependent enzymes that produce NO in nanomolar quantities for brief intervals of time which are critical for the normal cell biological functions as vasodilatation or neurotransmission regulation; while the inducible NOS (iNOS) is not constitutively expressed in cells but caused primary in the inflammatory states by cytokines at large NO amounts that last until the enzyme degradation and are critical for the inflammatory and immunological response to the incursive pathogens, therefore, the overexpression of NO was involved in many pathogeneses as explained by **Hussein et al. (2022)**. Overdosing of paracetamol is known to be related to inflammation and NO upregulation from macrophages and hepatocytes (**Yousef et al., 2010; Hussein et al., 2022)**. And mice deficient in iNOS were less responsive to paracetamol hepatotoxic action compared to wild-type mice as revealed in **Abdel-Zaher et al. (2007)**.

Under this status, it is conceivable that the protective activities of natural products based on safe and efficient CYP2E1 inhibitors that can modulate greater CYP2E1 activity plus decrease the harmful influence of created hazardous metabolites through free radical scavenging, and or antioxidant and anti-inflammatory effects related to their phenolic compound functions could be considered **(Attaullah et al., 2023; Sarkar et al., 2022; Naggayi et al., 2015)**.

Table (2): Protective effect of silymarin drug, clover bee honey alone and bee honey combined with 3% propolis, pollen, royal jelly or their mix on serum total antioxidant capacity, lipid peroxidation as MDA and nitric oxide in rats received paracetamol overdose.

	C-	C+	SD	H	H-Pro	H-Pol	H-RJ	H-M
TAC (ng/ml)	2.9 ± 0.1 ^{a}	0.6 ± 0.05 ^{b}	2.86 ± 0.34 ^{a}	2.82 ± 0.28 ^{a}	2.9 ± 0.2 ^{a}	2.86 ± 0.14 ^{a}	2.91 ± 0.19 ^{a}	2.88 ± 0.22 ^{a}
MDA (Mmol/l)	1.68 ± 0.91 ^{d}	11.39 ± 1.51 ^{a}	6.37 ± 0.81 ^{b}	5.6b ± 0.4 ^{c}	4.41 ± 0.41 ^{c}	4.87 ± 0.44 ^{c}	5.05 ± 0.36 ^{bc}	4.62 ± 0.38 ^{c}
NO (U/l)	2.63 ± 0.24 ^{e}	6.42 ± 0.58 ^{a}	4.09 ± 0.41 ^{b}	3.57 ± 0.2 ^{bc}	3.51 ± 0.31 ^{bc}	2.78 ^{de} ± 0.2	3.5 ± 0.3 ^{bc}	3.31 ± 0.29 ^{cd}

Data are expressed as mean ± standard deviation. Values within a row having different super scripts are significantly different ($p \leq 0.05$) as indicated by one-way ANOVA followed by Duncan's multiple range test (a > b > c > d > e > f).

SD: silymarin drug; H: clover bee honey alone; H-Pro: honey + 3% propolis; H-Pol: honey with 3% pollen; H-RJ: honey with 3% royal jelly; H-M: honey with 3% equal mix of propolis, pollen and royal jelly.
TAC, total antioxidant capacity; MDA, malondialdehyde; NO, nitric oxide.

Total antioxidant capacity (TAC) was elevated markedly by each of the silymarin drugs and consumption of either bee honey alone (H) or combined with 3% of its different products as 5 g/kg body weight, which didn't significantly change from each other and when compared with a healthy group also.

There are significant decrements regarding MDA and NO results for each of the silymarin drug (SD) groups and all honey groups compared to the control + group (C+). But it's worth observing generally that these improvements were more done for various honey groups than the SD group by significant changes in some times, and adding different honey products to the honey enlarged good effects than honey alone by significant effect some times. Although MDA decreases showed nonsignificant changes between the honey alone group and groups of honey plus various it's products, however, it is significantly lower than either C+ or SD group except for honey with royal jelly (H-RJ) which wasn't significantly different from SD group. It could be noticed concerning NO results significant reduction for honey with pollen group (H-Pol) than SD group that didn't significantly different from the healthy group and group of H-M (honey with an equal mix of propolis, pollen, and royal jelly as 3%) also, reflecting the best effect.

Silymarin, a natural flavonolignan extract from *Silybum marianum* has been widely used as a proven antioxidant agent against various toxicities and used to treat liver disorders **(Sarkar et al., 2022)**. Also, silymarin is a recognized CYP2E1 inhibitor **(Pingili et al., 2019)**. Silymarin at this study dose (50 mg/Kg body weight) is capable of protecting against oxidative stress and improving antioxidant status as showed by **Islam et al. (2021) and Sarkar et al. (2022)**. Also, **Galal et al. (2012)** showed that pretreatment with silymarin before paracetamol intake significantly lowered both oxidative stress and inflammatory cytokines.

Honey as a natural product and bee products (propolis, royal jelly, and pollen) have made the attention of researchers as supplemental and

alternative therapies due to their free radical scavenging and antioxidant activities related to their active substances like phenols (flavonoids and phenolic acids) enzymes, carotenes, terpenes, protein, amino acids, organic acids plus other minor ingredients which participate in their antioxidant actions and have biological effects in protecting anti various disorders and enhancing good health by mechanisms as the confiscation of free hydroxyl and superoxide radicals, hydrogen donation and chelation of metallic ion **(Nassar et al., 2020)**. In healthy individuals, 1.2 g/kg of honey enhanced the activity and concentrations of antioxidants such as glutathione reductase, β-carotene, and vitamin C **(Al-Waili, 2003)**.

Honey, propolis plus royal jelly, and bee pollen are from the natural main source of chrysin, a flavonoid from flavone class members and has been reported to have many pharmacological properties as antioxidant, anti-inflammatory, anti-apoptotic plus had defensive effects anti various pathological conditions **(Mehrzadi et al., 2021, Naz et al., 2019, Kiribati et al., 2020 Kumar et al., 2024 and Denisow and Denisow-Pietrzyk 2016)**. Chrysin at different doses like 25, 50, and 100 mg/kg orally for different periods of 3 and 6 weeks demonstrated strong antioxidant action by lowering lipids peroxidation, raising antioxidants defense techniques by raising SOD (superoxide dismutase) activity and GSH (reduced glutathione) content **(Mehrzadi et al., 2021 and Kseibati et al., 2020)**. Additionally, the chrysin effect on decreasing NO (nitric oxide) content and iNOS (inducible nitric oxide synthase) while increasing the eNOS (endothelial NO synthase) protein expression as assessed by **Kseibati et al. (2020)**. Moreover, the results by **Pingili et al. (2019)** based on both rats in vivo and rat liver microsomes in vitro using oral administration of 80 mg/ kg paracetamol with 100 or 200 mg/kg chrysin for 15 sequent days showed that chrysin might be inhibited the CYP2E1, CYP3A4 and CYP1A2-mediated paracetamol metabolism; so decreased the NAPQI formation and protected liver plus kidney.

The presence of distinct phytoestrogenic isoflavonoids (such as genistein, daidzein, formononetin, biochanin A, and glycitein) within clover plants and consequently, at clover honey can provide specific bioactivities which should be furthermore researched (**Sultana et al., 2022)**. As well as royal jelly was also reported to contain isoflavonoids

(such as genistein, formononetin, and coumestrol) which are related to antioxidant, anti-inflammatory, and anti-apoptotic pharmacological properties **(Kumar et al., 2024)**. The antioxidant activities of genistein plus other phytoestrogen have been established in various animal and in vitro models as the protection anti peroxide or oxygen radicals formation by phorbol ester and mainly anti DNA oxidative damage by UV-radiation, likewise in animals, especially mice models, dietary genistein showed to stimulate endogenous antioxidants like SOD (superoxide dismutase), GSH_{-Px} (glutathione peroxidase), GSH_{-R} (glutathione reductase) and GST (glutathione S-transferase), plus the antioxidant actions by the defense against cell damage caused by free radicals through the metabolism of toxic oxidative intermediates (**Sultana et al., 2022)**. Moreover, it's important to mention that genistein significantly modulated the paracetamol-caused hepatic toxicity through inhibition of CYP2E1, rapid reinstatement of GSH accelerated and promoted glucuronidation of paracetamol plus antioxidant activities through activation of UGTs (uridine diphosphate glucuronosyltransferases) and expression of UGT mRNAs as investigated by **Fan et al. (2015)**. Similarly, results showed in rats by consumption of 120 mg/kg of product rich in soy isoflavones with genistein and daidzein being the major isoflavones for 2 weeks which reduced liver toxicity and the paracetamol-protein adducts formation in the liver by prohibiting cytochrome P-450-mediated bio-activation and GSH depletion while enhancing urine drug excretion (**Liu et al., 2016**). Moreover, the same line results were found based on studies in cultured cells in which genistein reduced the residual paracetamol contents and promoted the paracetamol metabolic transformation to glucuronic acid in human HepG2, Hep3b, and L-O2 cells via the Nrf2/Keap1 pathway after 24 hours of genistein treatment with a dosage-dependent manner **(Yuan-jing et al., 2016)**. Since, Nrf2 (nuclear factor erythroid 2-related factor 2) remains in cytoplasm via linking Keap1 (Kelch-like ECH-associated protein 1), while under oxidation stress it moves to the nucleus where causes genes transcription involved encoding antioxidative (like GSH resynthesis) and metabolic enzymes of phase II (like UGTs and GST), and this antioxidant response through Nrf2 way is the main cellular defense technique anti the oxidative stress cytotoxic effects **(Yuan-jing et al., 2016; Jaeschke and Ramachandran, 2024)**.

Besides this, the main fatty acids of royal jelly 10H2DA (10-hydroxy-2-decenoicacid) and SA (sebacic acid) have anti-inflammatory properties by inhibiting inflammatory mediators (like NO and IL-10), and regulating proteins in the NF-$_K$B signaling (Nuclear Factor kappa-B) and MAPK (mitogen-activated protein kinase) pathways that lead to inhibition of inflammatory genes (like IL-1, IL-6, COX-2, and MCP-1) **(Kumar et al., 2024)**.

Moreover, kaempferol a flavanol reported to be found in bee pollen, royal jelly, and propolis **(Denisow and Denisow-Pietrzyk, 2016; Kumar et al., 2024 and Lesmana et al., 2024)**, protective liver anti-paracetamol toxicity at (250 mg/kg) for 1 week through its antioxidant, anti-inflammatory and anti-apoptotic actions since significantly increased the hepatic GSH and SOD, while suppressed MDA and ROS levels by CYP2E1 inhibition plus affected many transcription factors involved in inflammation as NF-$_K$B (Nuclear Factor kappa-B) **(BinMowyna and AlFaris 2021)**. Also, CAPE, a caffeic acid phenethyl ester that was reported to be found in both bee pollen and propolis **(Denisow and Denisow-Pietrzyk, 2016; Kumar et al., 2024; Lesmana et al., 2024)**, showed antioxidant, anti-inflammatory properties against paracetamol hepatotoxicity at 10 µg/kg **(Kamis and Çoban, 2019)**.

Regarding p-coumaric acid, the strong antioxidant and the most prevalent hydroxycinnamic acid isomer in nature **(Cha et al., 2018)** that noticed as the primary phenolic compound in Egyptian clover honey ethanolic extract, contributing about 83.0% **(Roby et al., 2020)**, it suppressed paracetamol-induced hepatic apoptosis through ROS-mediated DNA injury responses plus inflammation through modulating the MAPK (mitogen-activated protein kinase) signaling axis **(Cha et al., 2018)**. while when examining its inhibitory effect on cytochrome CYP450 enzyme on rat liver microsomes in vitro, it had not significantly inhibited the CYP2E1 and CYP2C11activities and a weak inhibitory effect on CYP3A4 and CYP1A2 **(Ma et al., 2023)**.

Also, it’s important to mention that autophagy is a cellular degradation process to remove and prevent the accumulation of modified molecules afterward cellular stress, and autophagy dysregulation is implicated in many disorders and diseases related to inflammation and oxidative stress in which the autophagy down-regulation and up-

regulation modulated via ROS have been demonstrated to have either negative or beneficial effects. Propolis or its bioactive components like p-coumaric acid, chrysin, kaempferol galanin, and CAPE (caffeic acid phenethyl ester) can change cellular autophagy by affecting the expression of transcription factors and proteins linked to autophagy; plus, indirect dual function in cellular redox equilibrium that involves affecting ROS, TAC, GSH, and GPX levels and modulating Nrf2, and through affecting inflammatory signaling ways linked autophagy and its components like IL-6, TNF-α, IL-1 β, and MAPK/NF-κB pathway. By these activities of propolis, it can serve as an efficient adjuvant treatment in conditions linked to inflammation and oxidative stress and it is an interesting subject for future searches considering the propolis variability in terms of bee types, geographical sources, and the bioactive compositions as explained in **Lesmana et al. (2024)**.

As for bee pollen's antioxidant and anti-inflammatory effects, **Denisow and Denisow-Pietrzyk (2016)** explained that bee pollen's antioxidative activities anti electrophiles and oxygen radicals contribute to its contents of anti-oxidant enzymes plus secondary plant metabolites as carotenoids, vitamin E, vitamin C, glutathione, plus phenols and flavonoids substances like CAPE (caffeic acid phenethyl ester), chrysin, galangin, kaempferol, quercetin, rutin, pinocembrin, apigenin, and isorhamnetin. Also, bee pollen components play a vital function in defending hosts against inflammatory reactions and invaded pathogens; and the anti-inflammatory techniques are linked to the existence of phytosterols and fatty acids, plus the quercetin activity inhibits the metabolism of arachidonic acid since a decrease in arachidonic acid levels lowers the proinflammatory prostaglandins levels and provides the anti-inflammatory effect, additionally the bee pollen biocomponents effects on cell function may be stimulating or inhibiting protein phosphorylation then later cell signaling pathways involving cell proliferation inhibition.

This information indicates that adding honeybee products such as propolis, royal jelly, pollen, or their mix to honey enlarges its nutritional and bioactive components increasing antioxidant, anti-inflammatory, and other biological activities (e.g CYP2E1 inhibition, autophagy modulation and decreasing the hazardous metabolites harmful) that promoting health

and can avoiding drugs toxicology, which being an interesting topic to investigate and still need a specific search, especially on little studied Egyptian honey types and its products considering the variation in bioactive compounds and their amount related to types of bees, floral origin, geographical area and season and contributing with the bioactivities that help in many disorders and diseases.

Protective effect of silymarin drug, clover bee honey alone and bee honey combined with 3% propolis, pollen, royal jelly or their mix on liver enzymes, protein fraction profile and relative liver weight in rats received paracetamol overdose.

As stated in **table (3)** that focusing on liver function, it could be significantly detected the elevation of all liver enzymes with less levels of total protein, albumin, and ratio of albumin/ globulin (A/G) as well as elevated globulin level than that of normal rats by administration paracetamol overdose as 650 mg/kg body weight for 2 weeks. This, in addition to significantly less in body weight gain (BWG%) and elevated relative liver weight than that of the c-group.

The liver is usually and unquestionably the organ most affected by paracetamol acute poisoning **(Bertolini et al., 2006)**. Paracetamol overdose caused hepatotoxicity were observed by biochemical measures plus histopathological changes in many studies that used paracetamol at various doses and duration as **Abdel-Zaher et al. (2007)** who used paracetamol by both a single acute toxic dose at 2.5 g/kg b.wt. and a smaller toxic dose 750 mg/kg b.wt. for 1 week. Elevating liver enzymes levels are an indicator of liver tissue necrosis due to the enzymes come out into the blood which has been detected in previous studies that used paracetamol at the same dose and duration of this study as **Yousef et al., (2010), Islam et al., (2021), Attaullah et al., (2023) and Abduh et al., (2023)**. **Dear (2024)** revealed that a noticeable release in AST and ALT activity is from the features of paracetamol toxicity, which usually happens 3-4 days next ingestion and the liver damage degree is related to the rate of ALT rises, but the spike size is not prognostic. As for, protein profile which descripted by lowering levels of total protein, albumin and albumin/ globulin ratio plus increased levels of globulin was found by searches as **Abduh et al. (2023)** who used paracetamol at the same dose and duration of this study and **Sarkar et al. (2022)** who used paracetamol

at once toxic dose of 2g/ Kg body weight. **Yousef et al. (2010)** indicated that the majority of serum proteins are mostly derived from the liver with albumin which being the much prevalent plasma protein making over 60% of serum total protein and involved in numerous physiological functions; and hypoalbuminemia by paracetamol due to a lesser extent in the amount of albumin synthesis cells in the liver via necrosis plus inflammation which cause albumin mRNA reduction by up to 90% through inflammation. Furthermore, **Sarkar et al. (2022)** revealed that hypoalbuminemia and total protein drop in serum are common liver illness symptom and the degree of cellular failure or the hepatopathy severity was related to the decreased levels of total protein. Also, lowering BWG and increasing liver or relative liver weight were detected by paracetamol administration at different doses and duration in many searches as **Islam et al. (2021) and Sarkar et al. (2022)**, in which oxidative stress conditions related to increase the weights of the kidney and liver and changed their biochemical indicators **(Nassar et al., 2020)**.

Oxidative stress is considered one of the main techniques by which paracetamol overuse causes liver damage, as previously explained via depleting levels of glutathione and tocopherol due to the concentration of highly reactive metabolite compound (NAPQI) then ROS formation plus high reactive peroxynitrite in which hepatic iNOS levels was increased **(Yousef et al., 2010; Attaullah et al., 2023; Dear, 2024; Jaeschke and Ramachandran 2024)**. These highly reactive oxidative stress modifies mitochondrial proteins by tyrosine nitration and the formation of nitrotyrosine on mitochondrial proteins causes at end DNA fragmentation and ultimately hepatocyte necrosis **(Sarkar et al., 2022; Jaeschke and Ramachandran 2024**). Moreover, **Aboshama et al. (2024)** indicated to the rapid and noticeable liver GSH depletion during pregnancy. The clearance of ROS by antioxidants was needed to reduce the adverse effects of oxidative stress on liver **(Sarkar et al., 2022)**.

Liver is the main important organ in the body since plays various biological works as detoxification, digestion and metabolism and any liver disease considers a global issue as seriously affects general health **(Islam et al., 2021; Sarkar et al., 2022)**. Natural products and their derivatives may be a viable choice to manage different types of liver disorders and diseases **(Islam et al., 2021)**.

Although there are no significant changes in AST levels for SD group and all honey groups compared to either C- or C+ groups, there are significant decreases in remaining liver enzymes of ALT, GGT and LDH in SD and all honey groups related to C+ group. It's worth mentioning that adding of different honey products to the honey supported hepatoprotective effects since ALT levels for honey plus it's different products reaching to insignificant levels from normal rats by perfect action for H-Pol which significantly lowered ALT in addition to LDH levels than SD reaching to insignificant levels of normal rats. Also, H-Pol and H-RJ recorded the best GGT levels that didn't significantly change from each of SD and normal groups; while honey alone has less significant improvement in GGT level than SD and didn't showed any significant changes between it and H-Pro and H-M. Regarding to albumin levels, there are significant elevation in it for SD and all honey groups compared to C+ group by nonsignificant changes between each other. While the improvements in total protein and globulin level for SD group and all honey groups did not significantly changes between each other and compared to either C- or C+ groups. A/G ratio for honey alone or combined with its different products significantly elevated than that of SD and the best effect achieved in H-Pro which didn't significantly differ from remain honey groups. Come in parallel with this results the improvement on BWG% which the highest effect even than that of SD and honey alone detected for H-Pro and H-M groups that didn't significantly different from C- group. Despite liver% for SD and all honey groups reaching to insignificant levels from healthy rats, it could be observed that the perfect liver weight record for SD and H-Pol groups.

Anyway H-Pol group seems to achieve the perfect hepatoprotective effect against paracetamol overdose in most of liver biomarkers that comes in parallel with nitric oxide results.

Silymarin, a natural flavonolignan extracts from *Silybum marianum* have been widely used as proven antioxidant agents against various toxicities and used to treat liver disorders **(Sarkar et al., 2022)**. Also, silymarin is a recognized CYP2E1 inhibitor and then reducing the concentration of highly reactive metabolite compound (NAPQI) and protecting liver (**Pingili et al., 2019)**.

Table (3): Protective effect of silymarin drug, clover bee honey alone and bee honey combined with 3% propolis, pollen, royal jelly or their mix on liver enzymes, protein fraction profile and relative liver weight in rats received paracetamol overdose.

	C-	C+	SD	H	H-Pro	H-Pol	H-RJ	HM
AST (U/l)	156 ± 12 ^{b}	192 ± 26 ^{a}	180 ± 15 ^{ab}	178 ± 13 ^{ab}	172 ± 17 ^{ab}	161.3 ± 13.05 ^{ab}	170.5 ± 13.5 ^{ab}	169 ± 14 ^{ab}
ALT (U/l)	41 ± 4.2 ^{d}	58 ± 3.2 ^{a}	50 ± 3.3 ^{b}	49 ± 3.5 ^{bc}	45 ± 4.3 ^{bcd}	42 ± 4 ^{cd}	44 ± 4 ^{bcd}	45 ± 3 ^{bcd}
GGT (U/l)	5.93 ± 0.15 ^{c}	11.9 ± 0.9 ^{a}	6.3 ± 0.6 ^{c}	8.9 ± 0.7 ^{b}	7.8 ± 0.7 ^{b}	6.15 ± 0.45 ^{c}	6.2 ± 0.55 ^{c}	8 ± 0.73 ^{b}
LDH (U/l)	920 ± 80 ^{d}	1749 ± 141 ^{a}	1510 ± 141 ^{b}	1451.7 ± 114 ^{b}	1153.7 ± 106 ^{c}	1010 ± 110 ^{cd}	1133 ± 110 ^{c}	1137 ± 103 ^{c}
TP (mg/dl)	7.4 ± 0.6 ^{a}	6.1 ± 0.6 ^{b}	7.1 ± 0.73 ^{ab}	6.9 ± 0.75 ^{ab}	7 ± 0.66 ^{ab}	6.8 ± 0.65 ^{ab}	7.3 ± 0.7 ^{ab}	7.1 ± 0.5 ^{ab}
Albumine (A) mg/dl	3 ± 0.34 ^{a}	0 .8 ± 0.14 ^{c}	2.2 ± 0.24 ^{b}	2.2 ± 0.21 ^{b}	2.4 ± 0.18 ^{b}	2.25 ± 0.21 ^{b}	2.4 ± 0.25 ^{b}	2.35 ± 0.2 ^{b}
Globulin (G) mg/dl	4.4 ± 0.26 ^{b}	5.3 ± 0.46 ^{a}	4.9 ± 0.49 ^{ab}	4.63 ± 0.43 ^{ab}	4.6 ± 0.48 ^{ab}	4.55 ± 0.44 ^{ab}	4.9 ± 0.45 ^{ab}	4.75 ± 0.3 ^{ab}
A/G ratio	0.681 ± 0.037 ^{a}	.151 ± 0.002 ^{e}	0.449 ± 0.005 ^{d}	0.519 ± 0.025 ^{bc}	0.523 ± 0.016 ^{b}	0.495 ± .002 ^{bc}	0.489 ± 0.006 ^{c}	0.494 ± 0.011 ^{bc}
Liver%	3.04 ± 0.16 ^{bc}	5.4 ± 0.4 ^{a}	2.8 ± 0.2 ^{c}	3.3 ± 0.25 ^{b}	3.1 ± 0.24 ^{bc}	2.8 ± 0.2 ^{c}	3.2 ± 0.24 ^{bc}	2.9 ± 0.21 ^{bc}
BWG%	51.8 ± 3.1 ^{a}	23.83 ± 1.77 ^{f}	36.26 ± 3.04 ^{e}	39.2 ± 2.9 ^{de}	49.49 ± 3.11 ^{abc}	43.9 ± 2.9 ^{cd}	45.8 ± 3.5 ^{bc}	50.1 ± 4.4 ^{ab}

Data are express ed as mean ± standard deviation. Values within a row having different super scripts are significantly different ($p \leq 0.05$) as indicated by one-way ANOVA followed by Duncan's multiple range test (a > b > c > d > e > f).

SD: silymarin drug; H: clover bee honey alone; H-Pro: honey with 3% propolis; H-Pol: honey with 3% pollen; H-RJ: honey with 3% royal jelly; H-M: honey with 3% royal jelly of equal mix of propolis, pollen and royal jelly.

AST, aspartate amino transferase; ALT, alanine amino transferase; GGT, gamma-glutamyl transferase; LDH, lactate dehydrogenase; TP, total protein; BWG, body weight gain.

Preventive effects of honey and other bee products anti hepatic damage and a synergistic effect may be considered, and the action mechanisms may be related to the antioxidant and anti-inflammatory functions of bee products, in which honey, pollen, propolis and royal jelly had improving effects anti hepatic toxicity in rats by sumithion insecticide and altered the raises in liver enzymes LDH, ALP, and γ-GT

(Nassar et al., 2020); as well as parallel results were found in CCl_4-induced model **(Saral et al., 2016)**.

Also, **Galal et al. (2012)** showed that honey can be served as an efficient hepatoprotective agent anti paracetamol-caused hepatic injury, since pretreatment by honey or silymarin before paracetamol intake noticeably prevented from the raises in serum hepatic enzymes levels, and lowered both inflammatory cytokines and oxidative stress, plus lowered the occurrence of paracetamol-caused liver lesions in histopathological evaluation. Results by **Mahesh et al. (2009)** suggested that the Indian honey protects liver against oxidative damage by paracetamol as assessed via biomarker plus histological analysis and it could be served as an efficient hepatoprotection. Moreover, **Gohar et al. (2020)** found that the adverse effects of high fat diet on liver enzymes and liver steatosis are altered in rats by treatment with acacia honey at high (2g/kg) and low (1g/kg) dosages for 4 weeks with more obvious effects for high dose which indicating the liver's metabolic adjustment to normal energy homeostasis physiology, this in addition to the improvements in liver cellular architecture; also this study showed the possible techniques of natural honey to effect on hepatic expressions of 3 metabolizing genes of lipids as fatty acid binding protein 1 (Fabp1) since honey noticeably downregulated the Fabp1(L-FABP) expression that inhibited cholesterol and long chain fatty acids uptake in living cells while the Fabp1 (L-FABP) up-regulation facilitates more fatty acids transportation to hepatocytes, which then induces steatosis and this results come in parallel with the finding that overexpression of L-FABP in patients with simple steatosis was obvious than non-steatosis patients. The natural honey role on the L-FABP gene expression is a new aspect that need more studies on humans to detect honey efficiency as a fatty liver disease treatment.

Denisow and Denisow-Pietrzyk (2016) reported that pollen extracts reduced blood values of ALT, AST, ALP and bilirubin in the poisoned individuals with drugs (as paracetamol or hydrocortisone) or with organic components (as ethanol, CCl_4, ethionine, trichlorethylene, or ammonium fluoride), as well as pollen bioactive compounds corrected liver function on many animals studies since the bee pollen detoxification effects have been detected in intoxicated rats with pesticides or heavy metals; so

extracts of bee pollen are advocated in chronic and acute inflammatory states, initial degenerative disorders, plus cholestatic hepatic illness, similarly after-traumatic or in toxic damage of liver. Also, bee pollen supplementation to diet results in enlarging body mass and strengthening muscles functions as found by **Salles et al. (2014)** which come in parallel with BWG results of this study.

It has been determined that royal jelly protects against paracetamol **(Kambur et al., 2009)**, CCl_4 **(Cemek et al., 2010)**, cadmium **(Cavusogluet al., 2009)**, and fumonisin **(El-Nekeety et al., 2007)** caused hepatic toxicity via its antioxidant activities **(El-Nekeety et al., 2007)**. Also, **Ahmed et al. (2014)** showed that royal jelly oral intake of 200 mg/kgB.W. for 2 weeks in rats showed obvious protection anti azathioprine-caused liver damage through lowering the high serum liver enzymes activities, blocking azathioprine-caused lipids peroxidation by lowering the formation of malondialdehyde and raising hepatic contents of GSH. Moreover, royal jelly has been found to contain a 57-kDa glycoprotein **(Zimmermann, 2002; Kumar et al., 2024)** which is thought to promote liver regeneration and hepatocyte formation **(Zimmermann, 2002)**.

Propolis hydro-ethanolic extract at 50 and 100 mg/kg.b.wt. dosages prevented anti 200 mg/kg.b.wt. of paracetamol-caused liver damage and loss body weight and may be useful for liver diseases management as showed by **El Menyiy et al. (2018)**. Also, Propolis at 50 mg/kg bw. prevents against 34 mg/kg bw. of aluminum caused rats hepatic damages as found by **Türkez et al. (2010)**. Consuming propolis in adults can induced a significant lower in AST, ALT, and ALP without leading to significant GGT changes as found by **Aliakbarian et al. (2024)**, as well as **Adeli et al. (2024)** showed that liver enzymes and glycemic indices in adults may be improved by propolis supplementation. Also, propolis has been demonstrated to prevent the liver plus improve HDL-C (high density lipoproteins-cholesterol) levels in patients with type-2 diabetes, as well as it showed preventive properties on hepatic steatosis and fibrosis for 54 patients taking propolis tablets at 250 mg twice daily as reviewed in **Tavares et al. (2022)**.

It’s worthy mention that paracetamol-caused protein adducts is considering an autophagy activation, which is a cellular process to

remove and prevent the accumulation of modified molecules after cellular stress; therefore, autophagy inhibition made paracetamol-caused hepatotoxicity even worse. while increasing autophagy has a protected action in this condition **(Jaeschke and Ramachandran, 2024)**. **Lesmana et al. (2024)** reported that too much ROS has been demonstrated to encourage apoptosis and inhibit autophagy; while propolis and its bioactive compounds like galangin, chrysin, kaempferol and p-coumaric acid can alter cellular autophagy by affecting the expression of transcription factors and proteins linked to autophagy; plus, indirect dual function in cellular redox equilibrium that involves affecting ROS, TAC, GSH and GPX levels and modulating Nrf2, and through affecting signaling pathways linked to inflammation; and this is an interest subject for future searches.

Also, as previously explained, the detoxifying and hepatoprotective activity of honey and its different products is associated with many bioactive compounds as fatty acids and polyphenols, mainly flavonoids and phenolic acids related to many activities like antioxidant, anti-inflammatory, anti-apoptotic and especially inhibited the cytochrome P-450-mediated paracetamol metabolism then decreased the NAPQI formation and protected liver such as chrysin, the promising flavonoid belongs to flavone class and widely present in honey, propolis, royal jelly and bee pollen; kaempferol, a flavonol reported to found in bee pollen, royal jelly and propolis; phytoestrogenic isoflavonoids (e.g., genistein and daidzein) in clover honey and royal jelly; CAPE, a caffeic acid phenethyl ester that reported to found in both bee pollen and propolis, royal jelly fatty acids of 10H2DA (10-hydroxy-2-decenoicacid) and SA (sebacic acid) and p-coumaric acid in Egyptian clover honey **(Mehrzadi et al., 2021; Kiribati et al.; 2020 Kumar et al., 2024; Denisow and Denisow-Pietrzyk 2016; Sultana et al., 2022; Fan et al., 2015; Roby et al., 2020; Cha et al., 2018)**.

In conclusion, adding honeybee product as propolis, royal jelly, pollen or their mix to honey enlarge its bioactive components and biological activities that possess a capability to attenuate paracetamol-induced toxicity.

Protective effect of silymarin drug, clover bee honey alone and bee honey combined with 3% propolis, pollen, royal jelly or their mix on

lipids profile and heart relative weight in rats received paracetamol overdose.

As obvious from results of **table 4**, high dose of paracetamol administration (600 mg/kg body weight for 21 days) induced dyslipidemia in rats characterized by significant elevation in serum levels of TG (total triglyceride), TC (total cholesterol), LDL-C (low density lipoprotein cholesterol), VLDL-C (very low-density lipoprotein cholesterol) and also each of AI (atherogenic index) and ACI (atherogenic combined index) , as well as significant reduction in serum HDL-C levels (high density lipoprotein cholesterol) compared to control negative group (C-). The atherogenic combination index (ACI) is a novel lipid bioindicator that, thoroughly evaluates the equilibrium between the blood antiatherogenic and atherogenic molecules to efficiently reflect the accumulative atherogenic impact and its correlation with the existence and intensity of coronary artery disease (CAD) as developed by **Toprak et al. (2024)**. Paracetamol at the dose and duration of this study was detected to cause unbalance between blood antiatherogenic and atherogenic molecules which reflected bad lipids profile by previous searches of **Islam et al. (2021), Attaullah et al. (2023) and Abduh et al. (2023)**. Cardiovascular risk may involve in paracetamol correlated adverse results **(McCraeet al., 2018)**.

Paracetamol injuries the liver and causes advancement of cholesterol circulation since it causes impairment in lipoprotein metabolism **(Okayed et al., 2018; Islam et al., 2021)**. The increasing cholesterol level by paracetamol toxication refers to hepatocyte necrosis and steatosis **(Attaullah et al., 2023)**. Also, **Islam et al. (2021)** showed that increasing TG level could be due to free acid availability, decreased lipoprotein release from the liver, and increased free acid esterification. This come in parallel with that finding by **Shi et al. (2019)** since treatment with paracetamol raised serum triglyceride (TG) levels and markedly exacerbated hepatic lipid buildup with the possible mechanism may be related to blocking autophagy linked to the AMPK/mTOR pathway, and lower dosages of paracetamol are recommended for patients with non-alcoholic fatty liver disease. Also, **Begriche et al. (2023)** suggested that common painkillers like paracetamol may be extra hepatotoxic with obesity and associated metabolic disorders and this disparity may result

from the degree of steatosis and obesity, the buildup of certain lipid species, or mitochondrial dysfunction. Decreasing cholesterol level considers a sign for liver healing **(Attaullah et al., 2023)**.

Table (4): Protective effect of silymarin drug, clover bee honey alone and bee honey combined with 3% propolis, pollen, royal jelly or their mix on lipids profile, atherogenic indices, heart relative weight and BWG% in rats received paracetamol overdose.

	C-	C+	SD	H	H-Pro	H-Pol	H-RJ	H-M
TG (mg/dl)	49 ± 4.8 ^{d}	100 ± 10.1 ^{a}	61 ± 5.3 ^{c}	79.8 ± 6.8 ^{b}	64 ± 6.0 ^{c}	66.5 ± 2.5 ^{c}	64 ± 4.0 ^{c}	56± 4.1 ^{cd}
TC (mg/dl)	89 ± 8.8 ^{b}	123 ± 8 ^{a}	100 ± 11 ^{b}	96.5 ± 8 ^{b}	97 ± 8.3 ^{b}	93 ± 5.7 ^{b}	97 ± 7.5 ^{b}	98 ± 5.7 ^{b}
HDL-C (mg/dl)	61 ± 5.7 ^{a}	39± 3.8 ^{b}	62± 6.4 ^{a}	53.5± 4.4 ^{a}	61± 5.6 ^{a}	56 ± 3.8 ^{a}	54 ± 4.7 ^{a}	59 ± 5.3 ^{a}
LDL-C (mg/dl)	18.2± 2.14 ^{d}	63.94 ± 2.09 ^{a}	25.8 ± 3.54 ^{c}	27.04 ± 2.24 ^{bc}	23.2 ± 1.5 ^{c}	23.7 ± 2.4 ^{c}	30.27± 2.66 ^{b}	27.83 ± 1.23 ^{bc}
VLDL-C (mg/dl)	9.8 ± 0.96 ^{d}	20.06 ± 2.11 ^{a}	12.2± 1.06 ^{c}	15.96± 1.36 ^{b}	12.8 ± 1.2 ^{c}	13.3 ± 0.5 ^{c}	12.83 ± 0.61 ^{c}	11.2 ± 0.82 ^{cd}
AI	0.459 ± 0.008 ^{d}	2.154 ± 0.1 ^{a}	0.613 ± 0.011 ^{c}	0.804 ± 0.002 ^{b}	0.59 ± 0.011 ^{c}	0.661 ± 0.011 ^{c}	0.796 ± 0.017 ^{b}	0.661 ± 0.05 ^{c}
ACI	2.35 ± 0.05 ^{f}	3.33 ± 0.02 ^{a}	2.57± 0.04 ^{e}	2.80 ± 0.03 ^{b}	2.58 ± 0.03 ^{e}	2.64 ± 0.02 ^{d}	2.70± 0.04 ^{c}	2.57 ± 0.001 ^{e}
Heart%	.301 ± .029 ^{d}	0.575 ± 0.035 ^{a}	0.351± 0.029 ^{cd}	0.433 ± 0.027 ^{b}	0.352 ± 0.025 ^{cd}	0.398 ± 0.012 ^{bc}	0.344 ± 0.028 ^{cd}	.326 ± 0.074 ^{d}

Data are expressed as mean ± standard deviation. Values within a row having different super scripts are significantly different ($p \leq 0.05$) as indicated by one-way ANOVA followed by Duncan's multiple range test (a > b > c > d > e > f).

SD: silymarin drug; H: clover bee honey alone; H-Pro: honey with 3% propolis; H-Pol: honey with 3% pollen; H-RJ: honey with 3% royal jelly; H-M: honey with 3% royal jelly of equal mix of propolis, pollen and royal jelly.

TG, triglyceride; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; AI (LDL-C + VLDL-C/HDL-C), atherogenic index; ACI (log 10 [Tri × "non-HDL-C÷HDL"]), atherogenic combined index.

In general, administration of SD and honey alone or honey with its various products significantly achieved good lipids profile in all previous biomarkers plus significant ameliorate in heart% than c+ group with nonsignificant changes between all honey groups each other and correlated to SD as well as C- groups for TC and HDL. By focusing on comparison between different groups, it could be also noticed that although SD group was significantly more effected than honey alone group in reduction of TG and VLDL, but all groups of honey plus its

different products recorded nonsignificant changes among each other or compared with SD group reaching to insignificant levels from C- group for H-M group which being the favorable effect on TG and VLDL. The less improvements in LDL and AI were detected for H-RJ which did not significantly different from honey alone group, while the best improvements achieved in remain honey groups of H-Pro, H-pol and H-M by insignificant changes among each other or compared with SD group. With respect to ACI, the perfect effect recoded for H-pro and H-M groups since didn't significantly change from SD group. As for heart%, groups of SD, H-Pro, H-RJ and H-M reached to insignificant levels from normal rats.

It could be concluded in general profile that groups of H-Pro and H-M have the perfect effect regarding to lipids profile. These results come in harmony with these of MDA biomarker results by perfect numeral reduction and chemical composition of total phenol and flavonoids in addition to fiber content since H-Pro and H-M being the highest levels for these components.

Silymarin, a natural flavonolignan extracts from Silybum marianum have been widely used as proven antioxidant agents against various toxicities **(Sarkar et al., 2022).** Silymarin at this study dose (50 mg/Kg body weight) capable to improve lipids profile **(Islam et al., 2021)**.

Treatment by high (2g/kg) and low (1g/kg) dosages of honey for 4 weeks considerably lowered TG, TC, LDL, VLDL scales and improved HDL levels in high fat diet feed rats to a greater degree than in normal diet feed rats, beside significantly reduced body weight-gain; also the potential mechanisms of natural honey effects on hepatic expression of three lipids metabolizing genes including fatty acid binding protein 1 (Fabp1), hepatic lipase (Lipc), and apolipoprotein A1 (Apoa1) was investigated in which the Fabp1 expression was considerably downregulated while that of Apoa1and Lipc were noticeably upregulated by acacia honey treatment with more prominent effects for high dose. The Fabp1(L-FABP) downregulation by honey inhibited cholesterol and long chain fatty acids uptake in living cells while the Fabp1 (L-FABP) up-regulation facilitates more fatty acids transportation to hepatocytes, which then induces steatosis and this results come in parallel with the finding that overexpression of L-FABP

in patients with simple steatosis was obvious than non-steatosis patients; and this is offer a honey protective role on liver. Regarding to the increased expression of Lipc by honey treatment indicates enhanced circulating lipids catabolism and lipids cellular uptake for usage in downstream processes leading to lower TG and LDL scales. moreover, HDL-C levels are more likely to rise when Apoa1 expression in the liver is restored following honey treatment since Apoa1 is the much prevalent protein component of HDL-C and its modulation can correlate with peoples as good plasma lipids profile and upper metabolites circulating level related to reduce atherosclerosis risk, as found and explained by **Gohar et al. (2020)**. The lipids lowering effects of natural honey as described by decreases in TC, TG and LDL are also seen in humans with obesity and metabolic syndrome compared with sucrose (**Yaghoobi et al., 2008; Terzo et al., 2020)**. Moreover, when honey is substituted for refined carbohydrates (fructose), rats are protected against fructose effects of hyper-triglyceride and peroxidation as described by a greater plasma α-tocopherol amount and ratio of α-tocopherol/triacylglycerol, plus reduce plasma NOx concentrations and heart lipid peroxidation **(Busserolles et al., 2002)**.

Focusing on bioactive components, P-coumaric acid, the strong antioxidant and the most prevalent hydroxycinnamic acid isomer in nature **(Cha et al., 2018)** that noticed as the primary phenolic compound in ethanolic extract of Egyptian clover honey, contributing about 83.0% **(Roby et al., 2020)**, it has been linked to some health promoting properties as antithrombotic activities and stimulate blood flow and because of this clover honey is advised to utilize in chronic venous disease **(Sultana et al., 2022)**. Also, Chrysin is a promising flavonoid from flavone class, widely and naturally present in honey, propolis plus royal jelly and bee pollen **(Mehrzadi et al., 2021, Naz et al., 2019, Kiribati et al., 2020 Kumar et al., 2024; Denisow and Denisow-Pietrzyk 2016)**, it has widely been employed in treatment of various degenerative disorders and for cardiovascular health related to its antioxidant and anti-inflammatory effects **(Naz et al., 2019)**.

Bee pollen extracts are reported to have beneficial effects in cardiovascular disease and removing swellings of cardiovascular due to its hypo-lipidemic effects by lowering total lipids, cholesterol, and

triacylglycerol contents; and these effects of bee pollen are linked to the free form of fatty acids (omega-3, a-ALA) found at higher than 50% in bee pollen, which function as a precursor for prostaglandin-3 being the primary inhibitor of platelets aggregation; also high activity of fibrinolytic system has been found after pollen intake and this property prevents against brain strokes and heart diseases as reviewed by **Denisow and Denisow-Pietrzyk (2016)**.

Both preclinical and clinical studies have reported that royal jelly lowers the sever of chronic illness and metabolic dysfunctions involving diabetes plus cardiovascular disorders by lowering cholesterol, improving blood vessel function and minimizing inflammation, oxidative stress and bad fat accumulation, related to its compounds like fatty acids and peptides as revealed in **Kumar et al. (2024)**.

Supplementing with propolis improves serum levels of HDL-C and LDL-C, which may slow the development of heart disease in adults with affecting on TG and TC. Propolis is recognized by people, accessible, and safe. It could be regarded as an extra treatment along with the utilized medications to control lipids profiles. **(Ahmed et al., 2024)**. Also, **Tavares et al. (2022)** revealed that propolis bioactive compounds have therapeutic benefits in vascular illnesses, acting on underlying disorders-linked states as inflammation, oxidative stress, dyslipidemia, hypertension and diabetes in which propolis products can also scavenge free radicals resulting in a reduction in lipid peroxidation and modulate blood lipid metabolism. Moreover, propolis has been found to reduce blood pressure and cholesterol amount **(Castaldo and Capasso 2002)**.

Its worthy mentioned that excessive exposure to ROS has been found to promote apoptosis and inhibit autophagy, which is a cellular process to remove and prevent the accumulation of modified molecules after cellular stress **(Lesmana et al., 2024)**. The paracetamol possible mechanism to raise serum TG levels and exacerbate hepatic lipids buildup may be related to blocking autophagy linked to the AMPK/mTOR pathway as showed by **Shi et al. (2019)**. propolis and its bioactive compounds can change cellular autophagy by affecting the expression of transcription factors and proteins linked to autophagy; plus, indirect dual function in cellular redox equilibrium that involves affecting ROS, TAC, GSH and GPX levels and modulating Nrf2, and through affecting inflammatory

signaling ways linked autophagy and its components like IL-6, TNF-α, IL-1 β, and MAPK/NF-κB pathway; and these activities are included in review by **Lesmana et al. (2024)** who revealed that Chinese and Brazilin propolis were found to attenuate apoptosis in HUVECs (human umbilical vein endothelial cells) associated with oxidized-LDL-induced damage by several mechanisms as modulating the autophagic pathway; as that doing by propolis bioactive compounds like p-coumaric acid, chrysin, galangin and kaempferol in several cell types since e.g. kaempferol induced autophagy via the AMPK-mTOR signaling pathway; and this is an interest topic for future searches.

This information provides that adding different bee products to honey enlarge its biological activities which still need more specific searches to prove and detect the perfect type of a cheap Egyptian honeys and its products, effective safe dose, form and period toward these respects considering the variation in bioactive components and their mechanisms.

Protective effect of silymarin drug, clover bee honey alone and bee honey combined with 3% propolis, pollen, royal jelly or their mix on kidney function and relative kidney weight in rats received paracetamol overdose.

The results of table (5) indicated to renal dysfunction resulting in paracetamol overdose as 600 mg/kg body weight for 21 days described by significant increasing levels of creatinine, urea and uric acid, in addition to significant elevation in relative kidney weight (kidney%). Paracetamol induced nephrotoxicity were detected via biochemical measures plus histopathological changes by other investigators findings at the same paracetamol dose and duration of this study as **Yousef et al, (2010) and Attaullah et al. (2023)**. In addition to, **Neelima et al. (2020)** who used 200 mg/kg paracetamol intraperitoneally for 2 weeks and found elevating creatinine, urea and uric acid plus degeneration of tubular epithelium with acute necrosis in histological analysis. Moreover, a woman was found to have elevated serum creatinine and urea after taking a therapeutic amount of paracetamol three days before to hospitalization (**Satirapoj et al., 2010**). Its worthy mention that in renal disorders, urea builds up because the rate at which serum urea is produced is higher than the rate at which it is cleared, while an increase of plasma creatinine is

only seen when there is significant harm to functional nephrons as revealed by **Yousef et al. (2010)**.

The renal is a second organ that is affected by paracetamol toxicity since kidney dysfunction in around 25% from hepatotoxicity cases plus over 50% from cases of hepatic failure and while the liver function disturbance peak develops 2-4 days next to paracetamol overuse, renal dysfunction becomes more noticeable after a 1 week, when it occurs, and returns in about 2–3 weeks to normal after ingestion **(Bertolini et al., 2006)**.

Although kidney injury is a critical prognostic factor whenever there is severe liver impairment clinically and nephrotoxicity is fewer prevalent than hepatotoxicity by paracetamol overuse, but it can happen without or little liver injury, so kidney impairment appear to be caused by the direct toxicity of renal tubules from paracetamol (**Naggayi et al., 2015; Dear, 2024**) and induced renal tubular injury and renal failure can potentially result in death for both people and experimental animals **(Naggayi et al., 2015; Attaullah et al., 2023)**. Moreover, **Aboshama et al. (2024)** showed that liver is not the primary organ damaged by paracetamol overdose since only the liver had a mild toxic effect whereas the kidney and brain had more serious lesions and changed biochemical markers in which necrotic alterations with elevated seral creatinine and urea levels are found.

The different reaches hypothesis towards the mechanism of reno-toxicity by paracetamol was discussed by **Abdel-Zaher et al. (2008), Naggayi et al. (2015) and Aboshama et al. (2024)** involving the NAPQI excessive production in the renal producing depletion of GSH and covalent binding with tissue nucleophiles since oxidative stress considers an essential pathogenic way of drug nephrotoxicity by a metabolic activation into extremely activated free radicals including superoxide plus oxygen reactivity species which encourage peroxynitrite production then protein nitration which could lead to further oxidative damage into protein, DNA and lipid, also the selectively renal accumulation of paracetamol, a nonsteroidal anti-inflammatory reno-toxins in human and animal is supposed to causing a biochemical reactions chain which finish in chronic or acute nephropathies, in addition to encourage hepatocyte pus renal apoptosis. Moreover, the affection of paracetamol on kidney

function by decreasing blood flow to renal, glomerular filtration ratio, sodium excretion plus excretion of prostaglandin E2 in both human and rat was also discussed in **Yousef et al. (2010)**.

Around the world, research is being done to find protective molecules that would give the liver, kidney, and other organs the best possible protection while causing almost no negative side effects while they are in use **(Naggayi et al., 2015)**. So natural products as honey and its products are traditionally utilized for mitigation of drugs or toxins caused hepatic and/or renal disorders.

Table (5): Effect of silymarin drug, clover bee honey alone and bee honey combined with 3% propolis, pollen, royal jelly or their mix on kidney function and relative kidney weight in rats received paracetamol overdose.

	C-	C+	SD	H	H-Pro	H-Pol	H-RJ	H-M
Creatinine (mg/dl)	0.5 ± 0.04 ^{b}	0.7 ± 0.6 ^{a}	0.59 ± 0.06 ^{b}	0.53± 0.04 ^{b}	0.55 ± 0.06 ^{b}	0.59 ± 0.04 ^{b}	0.59± 0.05 ^{b}	0.59 ± 0.03 ^{b}
Urea (mg/dl)	23.5 ± 2.3 ^{d}	38.5 ± 2.4 ^{a}	28.1 ± 2.4 ^{bc}	29.9± 1.4 ^{bc}	32.1 ± 3.3 ^{b}	25.7 ± 2.1 ^{cd}	32.7 ± 3.0 ^{b}	29.9 ± 2.1 ^{bc}
Uric Acid (mg/dl)	1.2 ± 0.13 ^{d}	2. 5 ± 0.18 ^{a}	1.6 ± 0.11 ^{b}	1.5 ± 0.1 ^{bc}	1.3 ± 0.12 ^{cd}	1.4± 0.09 ^{bcd}	1.2 ± 0.11 ^{d}	1.4± 0.08 ^{bcd}
Kidney%	0.598 ± 0.032 ^{c}	1.1 ± 0.1 ^{a}	0.618 ± 0.042 ^{bc}	0.717± 0.063 ^{b}	0.619 ± 0.051 ^{bc}	0.663± 0.057 ^{bc}	0.65± 0.05 ^{bc}	0.641± 0.059 ^{bc}

Data are expressed as mean ± standard deviation. Values within a row having different super scripts are significantly different ($p \leq 0.05$) as indicated by one-way ANOVA followed by Duncan's multiple range test (a > b > c > d > e > f).

SD: silymarin drug; H: clover bee honey alone; H-Pro: honey with 3% propolis; H-Pol: honey with 3% pollen; H-RJ: honey with 3% royal jelly; H-M: honey with 3% royal jelly of equal mix of propolis, pollen and royal jelly.

In general, it could be noticed the significant reduction in creatinine, urea and uric acid levels beside significant less of kidney% for SD and all honey groups than C+ group, indicating improvements in kidney function. Considering the comparison between different groups, creatinine and urea levels for all honey groups didn't significantly different from SD group reaching to insignificant changes from C- group in all honey groups for creatinine levels and in H-Pol only for urea levels being the best effect. According to uric acid results it's important to note that honey with its different products had more uric acid lowering effects than that of honey alone and SD groups, reaching in all honey plus its products groups to nonsignificant uric acid levels of normal rats and the

perfect level recorded for H-RJ group. As for kidney%, groups of honey combined with its various products didn't significantly different from each of SD and C- groups indicating to improvement than honey alone that didn't achieve insignificant change from C- group. It could be concluded that H-Pol was the perfect reno protective effect in general, while H-RJ was the strongest uric acid lowering effect.

Focusing on previous studies, **Abd El-Aziz et al. (2023)** showed that Saudi Sider honey (1.2 g/kg/day) for 2 weeks improved methotrexate-induced nephrotoxicity in rats by improving the kidney function markers and histopathological changes plus decreasing MDA and increasing enzymatic antioxidant activities, thus it can be utilized as an adjunct supplement for patients needing methotrexate therapy. Also, **Al-Yahya et al. (2013)** have stated that Saudi Sider honey improved CCl_4-caused nephrotoxicity by reducing rat's serum levels of creatinine, urea, uric acid and NO plus also the kidney's MDA contents, beside increased renal weight and GSH content, this in addition to improve the renal pathological injury of CCl_4 exposed rats as cell necrosis and intratubular infiltration and cloudy swelling.

The beneficial activities of bee pollen in removing swellings of renal due to its anti-inflammatory activity which linked to the prevalent of phytosterols and fatty acids have been reported in **Denisow and Denisow-Pietrzyk (2016)**. Propolis also is a rich bioactive compounds source and has kidney preventive effects, since propolis hydro-ethanolic extract at dosages 50 and 100 mg/kg.b.wt. prevented against paracetamol (200 mg/kg.b.wt.) induced impairment of kidney function and might be useful in the renal diseases management particularly proteinuria as showed by **El Menyiy et al. (2018)**. As well as **Tavares et al. (2022)** revealed that propolis could be utilized as a coadjutant natural treatment of proteinuria renal illness and has therapeutic efficacy in patients with diabetic and non-diabetic renal disease.

Honey, propolis plus royal jelly and bee pollen are from the main natural source of chrysin, the flavonoid belongs to flavone class and has been reported to has many pharmacological properties as antioxidant, anti-inflammatory, anti-apoptotic so it had defensive effects against various pathological conditions as nephrotoxicity **(Mehrzadi et al., 2021; Naz et al., 2019; Kiribati et al., 2020; Kumar et al., 2024; Denisow**

and Denisow-Pietrzyk 2016). Chrysin at different doses like 25, 50 and 100 mg/kg orally for 21 days attenuates nephrotoxicity induced by sodium arsenate in rats through suppressing oxidative stress and inflammation as malondialdehyde and nitric oxide and increasing antioxidants in kidney tissue plus improving kidney function as serum creatinine and urea levels. Moreover, the results by **Pingili et al. (2019)** based on both rats in vivo and rat liver microsomes in vitro using orally administration of 80 mg/ kg paracetamol with 100 or 200 mg/kg chrysin or silymarin (100 mg/kg) for 15 sequent days showed that chrysin might be inhibited the cytochrome P-450-mediated paracetamol metabolism; so decreased the NAPQI formation and protected liver plus kidney since the raised bio-markers of kidney and liver functions were markedly lowered by chrysin or silymarin when compared to control group of paracetamol which parallel with histopathological results.

These findings highlight detoxified effects of supported Egyptian clover honey with its different products against paracetamol toxicity, emphasizing the need for additional specific studies employ on variety of experimental models and human clinical trials to prove and detect the perfect type of a cheap Egyptian honeys and its products, effective safe dose, form and period toward these respects considering the variation of bioactive components and their mechanisms.

Sensory evaluation of jam prepared by replacing sucrose sugar with clover bee honey alone or plus 3% its different products.

Sensory evaluation of jam prepared by replacing sucrose sugar with clover bee honey alone or plus 3% its different products is presented in **Table (6)**. It could be observed that jam prepared with honey alone, H-Pol and H-RJ replacement recorded the favorable values in all sensory parameters and did not significantly differ from the control jam, but it is worth mentioning that, it come by numeral best levels. Also, H-M didn’t significantly different from control jam in all sensory evaluation markers, and at the same time when compared with the perfect jams of honey alone, H-Pol and H-RJ, it had nonsignificant changes for color, texture and overall acceptability but also it had less significant values for taste and flavor related to its content of propolis which showed less sensory evaluation because its taste.

Also, it is important to mention that all jams prepared by honey kept its texture without smoothing the surface or saccharification, indicating good technological properties than that of sucrose sugar. This, in addition to the marked observation of the lovely flavor of H-Pol which near to that of clove. Although, honey mixed with its different products can be used as it is or even by adding to the water for health purposes, but including it within different foods as jams or cake give more choices to consume plus enrich and take advantage of biological benefits of it and different additional ingredients of preparing food as fruits in jams which allowing to more consume it with more ease or satisfaction because of more different flavor, homogeneous consistency, easier spread ability, and its proportionality as a bread spread without drip. It is worthy mentioned that honey different products could be added in the final of preparing jams to avoid the effect of long heating on beneficial effects. Anyway, more technological studies are needed to prove this technological orientation and the effect of heating on the effectiveness of honey or its products and the convertible amounts depending on this to achieve the desired health benefits. This indicates that the honey combined with its different products can be used as it is or successfully used in the preparation of a modern functional foods as jams with high sensory and healthy benefits.

Table (6): Sensory evaluation of jam prepared by replacing sucrose sugar with clover bee honey alone or plus 3% its different products.

Parameter	Control	H	H-Pro	H-Pol	H -RJ	H-M
Appearance	9.3 ± 0.67 ^{ab}	9.5± 0.53 ^{a}	7.9 ± 0.88 ^{c}	9.1 ± 0.74 ^{ab}	9.5 ± 0.71 ^{a}	8.7 ± 0.7 ^{b}
Color	8.9 ± 1.1 ^{a}	9.0± 0.67 ^{a}	7.7 ± 0.68 ^{b}	9 ± 0.82 ^{a}	9.1 ± 1.1 ^{a}	8.3± 0.68 ^{ab}
Taste	7.9 ± 1.1 ^{ab}	8.4± 0.52 ^{a}	6.6 ± 0.53 ^{c}	8.4 ± 1.07 ^{a}	8.5 ± 0.97 ^{a}	7.3 ± 0.48 ^{b}
Flavor	8.3 ± 1.34 ^{ab}	9.0± 0.47 ^{a}	6.6 ± 0.53 ^{c}	8.5 ± 1.08 ^{a}	8.5 ± 0.97 ^{a}	7.5 ± 1.07 ^{b}
Texture	8.4 ± 1.17 ^{ab}	9.0± 0.67 ^{a}	7.6 ± 0.52 ^{b}	8.7 ± 0.82 ^{a}	8.8 ± 0.79 ^{a}	8.2± 1.03 ^{ab}
Overall acceptability	8.6 ± 0.84 ^{ab}	8.8 ± 0.63 ^{a}	7.3± 0.95 ^{c}	8.7± 0.68 ^{ab}	8.7 ± 0.68 ^{ab}	8± 0.42 ^{b}

Data are expressed as mean ± SD. Values within a same row having different superscripts are significantly different ($p \leq 0.05$); where the small letters indicate significant among different cake as indicated by one-way ANOVA followed by Duncan's multiple range test (a > b > c > d > e).
H: clover bee honey alone; H-Pro: honey with 3% propolis; H-Pol: honey with 3% pollen; H-RJ: honey with 3% royal jelly; H-M: honey with 3% royal jelly of equal mix of propolis, pollen and royal jelly.

As the world's first sweetener, honey is thought to be a healthier alternative to sugar and other sweeteners. It is frequently used to sweeten juices, coffee, and tea, but it can also be used in a variety of food products, as bakery products (bread, biscuits, muffins, and others), beverages (beverages of sport, fruit, vegetable, ice tea, yoghurt and chocolate milk), confections, jams, candy, marmalades, yogurts, spreads and others, highlighting that honey is a highly health and safe ingredient to use in food **(Predanócyová and Šedík 2024)**. The amount of honey consumed is comparatively low, even with the awareness about the health benefits of honey and the availability of safe and high-quality local honey **(Kowalczuk et al., 2023)**. Consumers may find honey with extra ingredients, like fruits or chocolates, to be more acceptability and suitability for jams or sweet spreads plus honey's health-promoting qualities are greatly enhanced by the inclusion of these substances **(Sowa et al., 2019)**.

Its worthy mentioned that the antioxidative activity of honey was drastically decreased by heat treatment, excepting royal jelly and propolis as found by **Nagai et al. (2001),** as well as water or ethanol extracts have noticeably more bioactive components content than the natural bee pollen as revealed in **(Denisow and Denisow-Pietrzyk, 2016)**, so use these bee products with honey in food products may be useful.

Also, there are new trends related to bee products which should be further consider, e.g. **Cheng et al. (2024)** referred to pollen as a potential key role in production of fermented foods as a main or additional activator or fermentation agent, creating opportunities for innovative product development, and showed that fermented pollen may have positive health effects by improving the nutrient profile, breaking down allergenic substances, increasing bioavailability, and supporting gut health; however, more research is needed to fully comprehend the underlying mechanisms. Additionally, propolis has shown to be a desirable source of bioactive substances for the creation of fortified products that may reduce the need for food artificial additives or the concentration of medicines as showed by **Tavares et al. (2022)** who offered additional advice on the use of propolis encapsulated compounds as dietary supplements or in combination with medications to prevent and treat the severity of chronic and acute illnesses, this is because encapsulation technology has been used to improve the product's

bioavailability, extend their shelf life, and shield them from external factors like elevated temperatures, oxygen, light and water plus avoid interference with product. Also, manufacturers of nutraceutical products should promote propolis bioactive components encapsulated in nano particles for usage as an adjuvant therapeutic for chronic health disorders and for fortification of food and beverages. A sustainable economy will be promoted by the creation of new encapsulated natural bioactive components of propolis, which will help to value byproducts and agro-food wastes.

All these new trends related to bee products need more specific technological investigations, as well as clinical studies on humans are necessary to prove its safety, efficacy, the most suitable dose, bioactive compounds quantity and concentration to assess their potential as an affordable application choice in the pharmaceutical and food sectors.

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