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ISSUE INFORMATION

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Issue Information

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EDITORIAL

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The ART and LOGIC of scholarly communication: Effective skills for publication and beyond

Yangming Martin Lo

Pages: 981-984 | First Published: 13 April 2022

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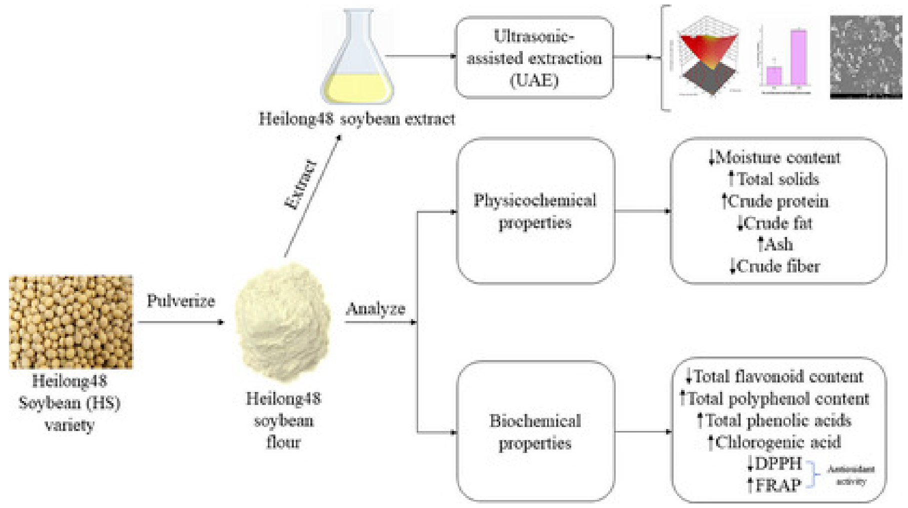
ORIGINAL ARTICLE

Open Access

Ultrasonic-assisted extraction of bioactive chlorogenic acid from heilong48 soybean variety: Parametric optimization and evaluation of physicochemical and bioactive properties

Nelson Dzidzorgbe Kwaku Akpabli-Tsigbe, Yongkun Ma, John-Nelson Ekumah, Juliet Osabutey, Jie Hu, Manqing Xu, Nana Adwoa Nkuma Johnson, Benjamin Kumah Mintah

Pages: 985-1002 | First Published: 11 March 2022



A satisfactory ultrasonic-assisted extraction model was obtained. The heilong48 soybean (HS) variety could be used to produce chlorogenic acid. There were protein–polyphenol interactions in the HS variety.

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REVIEW

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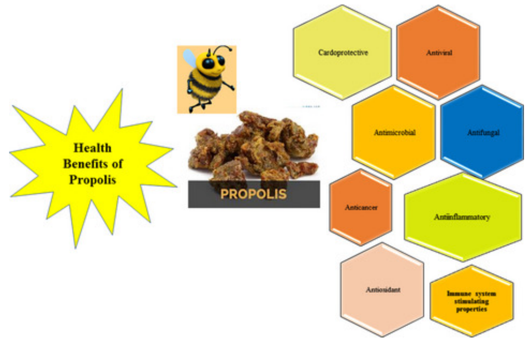
Does propolis have any effect on rheumatoid arthritis? A review study

Elyas Nattagh-Eshtivani, Naseh Pahlavani, Golnaz Ranjbar, Jamshid Gholizadeh Navashenaq, Ammar Salehi-Sahlabadi, Trias Mahmudiono, Mohammed Nader Shalaby, Mohammadhassan Jokar, Mohsen

Nematy, Hanieh Barghchi, Shahrzad Havakhah, Mona Maddahi, Mohammad Rashidmayvan, Maryam Khosravi

Pages: 1003-1020 | First Published: 10 March 2022



Rheumatoid arthritis (RA) is an autoimmune and systemic disorder, and cytokines and inflammatory responses play a key role in its pathogenesis. Antioxidant supplements may help reduce the symptoms and improve the quality of life in RA patients. Propolis has numerous antioxidant and polyphenolic properties and may exert beneficial effects on the oxidative stress biomarkers and inflammation process.

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ORIGINAL ARTICLES

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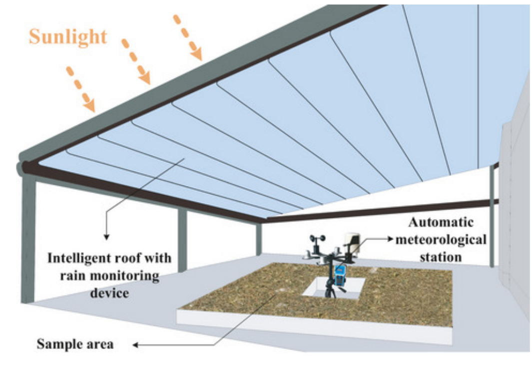
Moisture contents and product quality prediction of Pu-erh tea in sun-drying process with image information and environmental parameters

Cheng Chen, Wuyi Zhang, Zhiguo Shan, Chunhua Zhang, Tianwu Dong, Zhouqiang Feng, Chengkang Wang

Pages: 1021-1038 | First Published: 22 February 2022



In this study, images were captured continuously in the sun-drying process of Pu-erh tea. Environmental parameters (EP) of air humidity, air temperature, global radiation, wind speed, and ultraviolet radiation were collected with a portable meteorological station. Moisture contents and product quality of Pu-erh tea can be accurately predicted with deep learning-based methods. The proposed combinations of different environmental parameters can also provide a valuable reference in developing a new sun-drying system.

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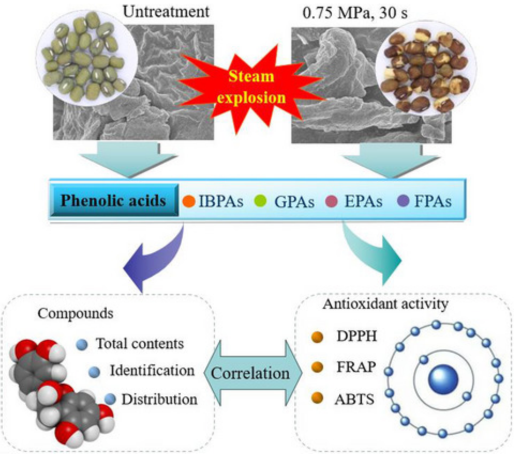
Steam explosion enhances phenolic profiles and antioxidant activity in mung beans

Fachun Wan, Chunyu Hou, Kaiyun Luo, Anwei Cheng

Pages: 1039-1050 | First Published: 22 February 2022



Steam explosion (SE) formed the large cavities and intercellular spaces of mung beans. SE increased the yields of insoluble-bound (IBPAs), glycosided (GPAs), esterified (EPAs) and free phenolic acids (FPAs). SE enhanced the antioxidant activity of IBPAs, GPAs, EPAs, FPAs in mung beans.

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Purification, antioxidant activities, encapsulation, and release profile of total flavonoids in Peony seed meal

Lixia Zan, Wangting Song, Weiwei Wang, Gang He, Xinsheng Li, Jinjin Pei

Pages: 1051-1057 | First Published: 21 January 2022

This present study focused on the purification, antioxidant activities, encapsulation, and release profile of total flavonoids in Peony seed meal. The result indicated that the encapsulated total flavonoid microcapsules are worthy for the development of functional foods and supplements, and Peony seed meal could be a potential resource in the food and pharmaceutical industries.

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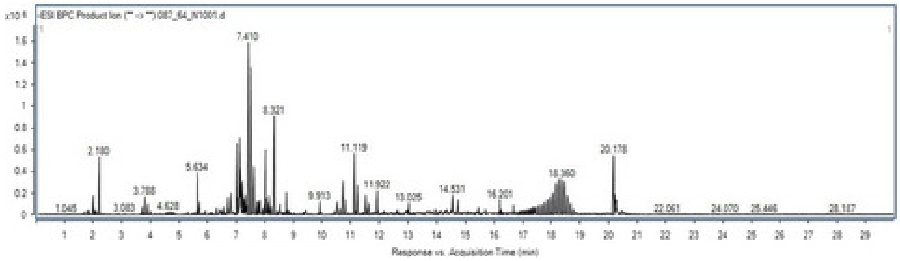
UHPLC-ESI-QTOF-MS^2 analysis of *Acacia pennata* extract and its effects on glycemic indices, lipid profile, pancreatic and hepatorenal alterations in nicotinamide/streptozotocin-induced diabetic rats

Hui Shao, Minmin Xiao, Zheng Zha, Opeyemi Joshua Olatunji

Pages: 1058-1069 | First Published: 19 January 2022



This study showed the beneficial effects of the *Acacia pennata* in controlling metabolic derangement, pancreatic and hepatorenal dysfunction in diabetic rats.

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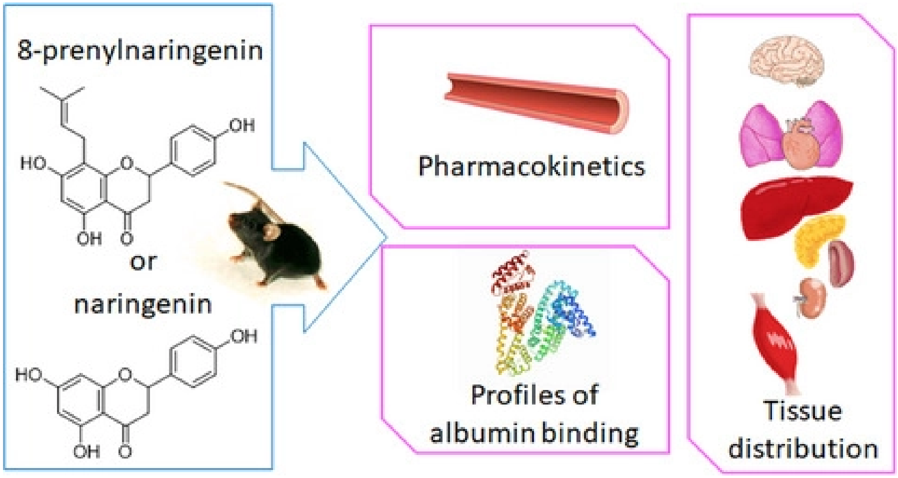
8-Prenylnaringenin tissue distribution and pharmacokinetics in mice and its binding to human serum albumin and cellular uptake in human embryonic kidney cells

Yoshiaki Tanaka, Hitomi Okuyama, Miyu Nishikawa, Shin-ichi Ikushiro, Mayumi Ikeda, Yu Ishima, Yuichi Ukawa, Kenichi Oe, Junji Terao, Rie Mukai

Pages: 1070-1080 | First Published: 22 January 2022



This study aimed to compare the parameters related to the bioavailability of 8-PN and its mother (nonprenylated) compound naringenin. The tissue distribution of 8-PN in mice was higher than that of naringenin. Compared with naringenin, 8-PN showed a stronger affinity to human serum albumin and higher cellular uptake in human embryonic kidney cells.

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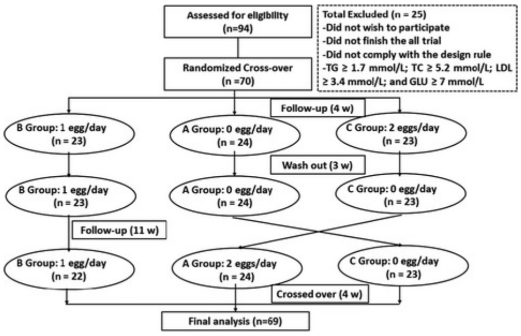
Daily intake of up to two eggs for 11 weeks does not affect the cholesterol balance of Chinese young adults

Zhili Ma, Wei Wu, Dexin Zhang, Ping Wu, Yuanhua Guo, Deyuan Li, Fang Yang

Pages: 1081-1092 | First Published: 17 January 2022



This study showed that a maximum of two eggs per day could not change the biomarkers associated with CVDs risk in young, healthy college students. Subjects who ate eggs at breakfast felt less hungry and more satisfied on the feeling of full day fullness.

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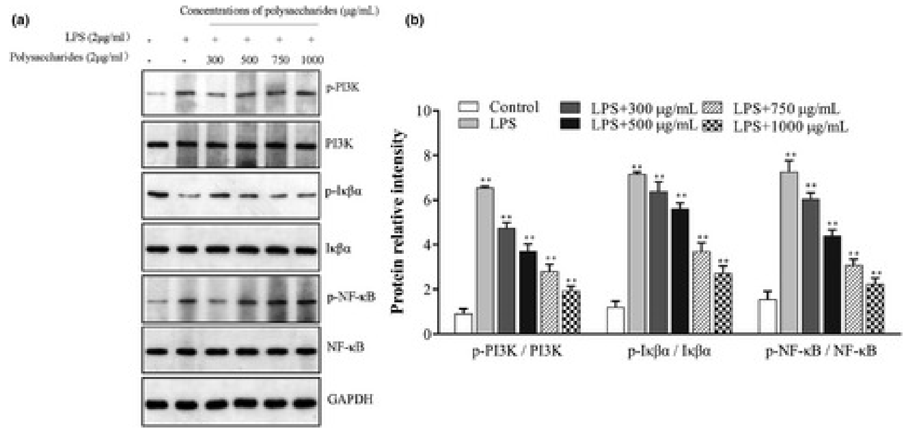
Immunomodulatory effects of the polysaccharide from *Sinonovacula constricta* on RAW264.7 macrophage cells

Zhidong Liu, Zhifang Liu, Laihao Li, Junjie Zhang, Qiancheng Zhao, Na Lin, Wenzhu Zhong, Mei Jiang

Pages: 1093-1102 | First Published: 25 January 2022



The immunomodulatory activities of a novel polysaccharide (SCP-1-1) from *Sinonovacula constricta* were examined in RAW264.7 cells. These findings could contribute to elucidate the immunomodulatory activities of the polysaccharide from *Sinonovacula constricta*.

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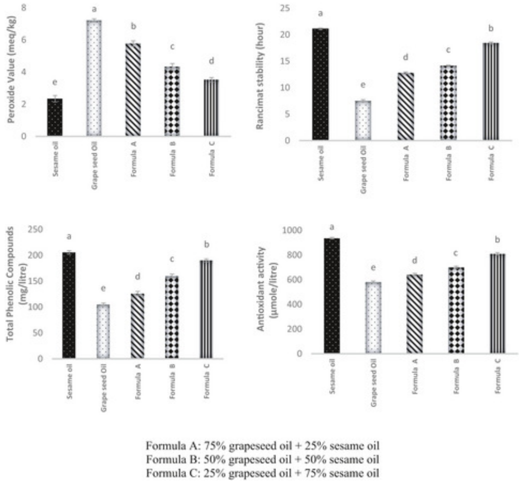
The oxidative and thermal stability of optimal synergistic mixture of sesame and grapeseed oils as affected by frying process

Maryam Khakbaz Heshmati, Maryam Jafarzadeh-Moghaddam, Akram Pezeshki, Rezvan Shaddel

Pages: 1103-1112 | First Published: 15 February 2022



Key findingsa) Mixing grapeseed oil with sesame oil can be a good way to improve the oxidative stability of grapeseed oil.b) The mixture of 75% sesame oil and 25% grapeseed oil as the optimum formulation had the best nutritional quality and lower cost.c) The optimum mixture of sesame oil and grapeseed oil is suitable to use as a cooking or salad oil and not for long-term frying.

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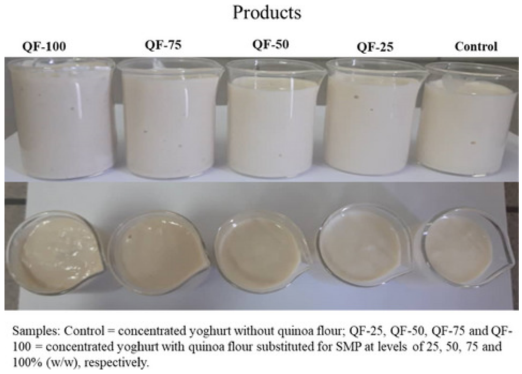
Quinoa flour as a skim milk powder replacer in concentrated yogurts: Effect on their physicochemical, technological, and sensory properties

Fatemeh Alkobeisi, Mohammad Javad Varidi, Mehdi Varidi, Majid Nooshkam

Pages: 1113-1125 | First Published: 24 February 2022



Samples: Control = concentrated yoghurt without quinoa flour; QF-25, QF-50, QF-75 and QF-100 = concentrated yoghurt with quinoa flour substituted for SMP at levels of 25, 50, 75 and 100% (w/w), respectively.

In this work, quinoa flour (QF; 0%, 25%, 50%, 75%, and 100% w/w) was used to replace skim milk powder (SMP) in concentrated yogurt.

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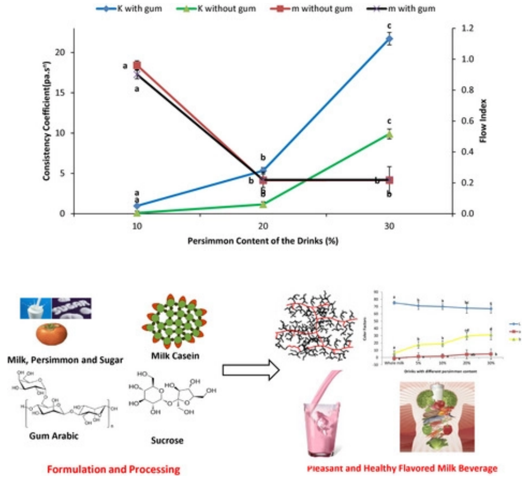
Formulation and production of persimmon milk drink and evaluation of its physicochemical, rheological, and sensorial properties

Akbar Jokar, Mohamad Hossyn Azizi

Pages: 1126-1134 | First Published: 11 February 2022



Different amounts of persimmon (5, 10, 20, and 30% W/V), gum Arabic (0.1 and 0.2% W/V), and sugar (3 and 5% W/V) were used to produce persimmon milk. By applying a proper content of persimmon in milk, we can produce a nutritious flavored milk drink with acceptable taste, stability, and consistency. As this drink has high nutrient contents like phenol, dietary fiber, vitamins, antioxidants etc., it can help promote health, especially of children.

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Predictors of the amount of intake of Ready-To-Use-Therapeutic foods among children in outpatient therapeutic programs in Nairobi, Kenya

Sophie Ochola, Irene A. Ogada, Colleta A. Odera

Pages: 1135-1145 | First Published: 18 January 2022

Two-hundred caregivers were assessed, where 73% of the children consumed the recommended amount of RUTF. A smaller proportion (54.4%) of children aged 6–11 months consumed the recommended amount of RUTF compared to older children. Predictors of amount of RUTF intake were child's birth order—firstborn (AOR 29.92; 95% CI: 5.67–157.93) and children's age; 12–17 months (AOR 5.19; 95% CI: 2.18–12.36) and 18–23 months (AOR 6.19 95% CI: 2.62) and caregivers' knowledge and practices in feeding a child with RUTF.

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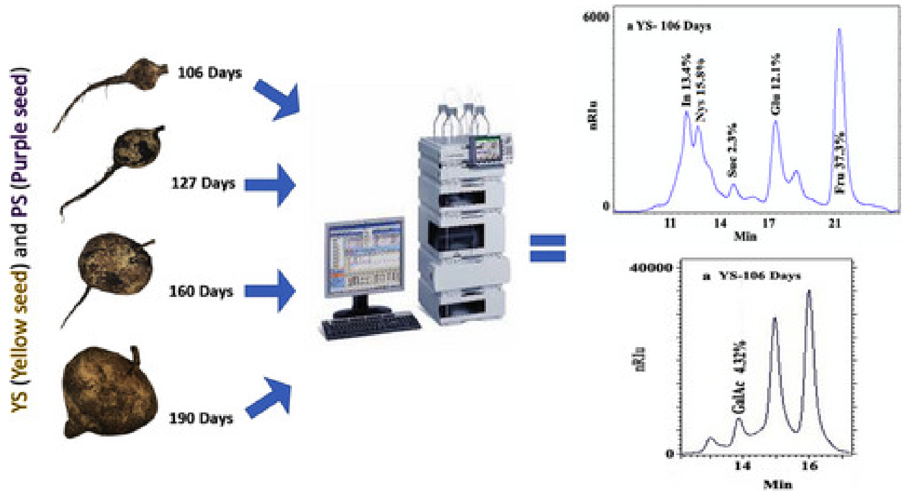
Polysaccharides of nutritional interest in jicama (*Pachyrhizus erosus*) during root development

Marcela González-Vázquez, Georgina Calderón-Domínguez, Rosalva Mora-Escobedo, Ma. Paz Salgado-Cruz, José Honorato Arreguín-Centeno, Ricardo Monterrubio-López

Pages: 1146-1158 | First Published: 23 January 2022



Study of Pachyrhizus erosus nutraceutical carbohydrates and glycemic index during root development. Pachyrhizus erosus nutraceutical carbohydrates are related to the state of maturity of the root, being inulin the first to be used. Pachyrhizus erosus root can be classified as a low glycemic index food.

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Identification of superior late-blooming apricot (*Prunus armeniaca* L.) genotypes among seedling-originated trees

Zeinab Mashhadi, Ali Khadivi

Pages: 1159-1166 | First Published: 18 January 2022

All the 48 late-blooming date apricot (*Prunus armeniaca* L.) genotypes could be useful as a parent to improve flowering season of cultivars. Also, among them, 10 genotypes were superior in terms of fruit quality-related characters, such as fruit weight, fruit color, and fruit taste, and thus they can be singled out for cultivation.

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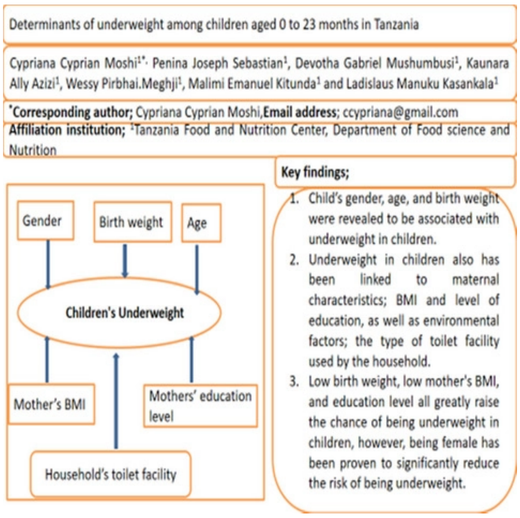
Determinants of underweight among children aged 0–23 months in Tanzania

Cypriana Cyprian Moshi, Penina Joseph Sebastian, Devotha Gabriel Mushumbusi, Kaunara Ally Azizi, Wessy Pirbhai Meghji, Malimi Emmanuel Kitunda, Ladislaus Manaku Kasankala

Pages: 1167-1174 | First Published: 18 January 2022



Determinants of underweight among children aged 0 to 23 months in Tanzania

Cypriana Cyprian Moshi[1*], Penina Joseph Sebastian[1], Devotha Gabriel Mushumbusi[1], Kaunara Ally Azizi[1], Wessy Pirbhai.Meghji[1], Malimi Emanuel Kitunda[1] and Ladislaus Manuku Kasankala[1]

[*]**Corresponding author;** Cypriana Cyprian Moshi,**Email address;** ccypriana@gmail.com

Affiliation institution; [1]Tanzania Food and Nutrition Center, Department of Food science and Nutrition

Key findings;

1. Child's gender, age, and birth weight were revealed to be associated with underweight in children.
2. Underweight in children also has been linked to maternal characteristics; BMI and level of education, as well as environmental factors; the type of toilet facility used by the household.
3. Low birth weight, low mother's BMI, and education level all greatly raise the chance of being underweight in children, however, being female has been proven to significantly reduce the risk of being underweight.

Underweight is recognized as an important indicator of health and nutritional status in the population. Determinants of underweight among children aged 0–23 months in Tanzania are not well documented. Secondary data analysis on a sample of 4327 children aged 0–23 months was done to determine factors that influence underweight in Tanzanian children.

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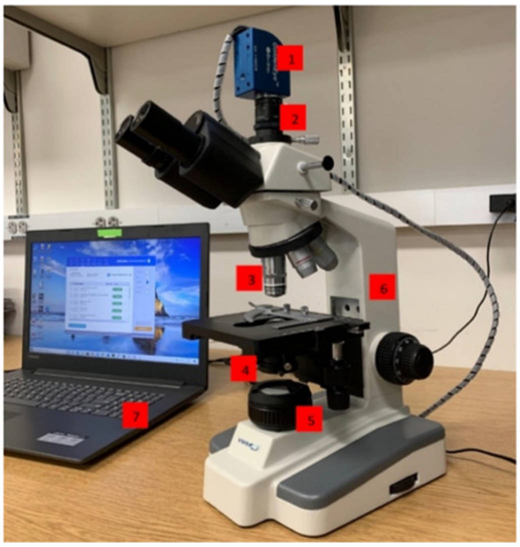
Developing an affordable hyperspectral imaging system for rapid identification of *Escherichia coli* O157:H7 and *Listeria monocytogenes* in dairy products

Phoebe Unger, Amninder Singh Sekhon, Xiongzhi Chen, Minto Michael

Pages: 1175-1183 | First Published: 18 January 2022

The objective of this foundational study was to develop and evaluate the efficacy of an affordable hyperspectral imaging (HSI) system to identify single and mixed strains of foodborne pathogens in dairy products. With the implementation of kNN (k = 3), overall classification accuracies of 58.97% and 61.53% were obtained for *E. coli* O157:H7 and *L. monocytogenes*, respectively.



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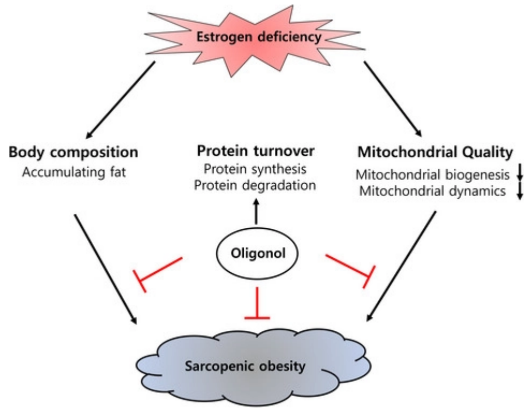
Effect of oligonol, a lychee-derived polyphenol, on skeletal muscle in ovariectomized rats by regulating body composition, protein turnover, and mitochondrial quality signaling

Jeong Hun Kim, Hyangkyu Lee, Ji Min Kim, Byung-Joo Lee, In-Joo Kim, Kyoungjune Pak, Yun Kyung Jeon, Keunyoung Kim

Pages: 1184-1194 | First Published: 11 March 2022



Oligonol is a low-molecular-weight polyphenol product derived from lychee (*Litchi chinensis* Sonn.) fruits. It empirically demonstrates the efficacy of the natural plant product oligonol in the amelioration of sarcopenic obesity associated with estradiol deficiency resulting from ovariectomy by regulating body composition, protein turnover, and mitochondrial quality signaling.

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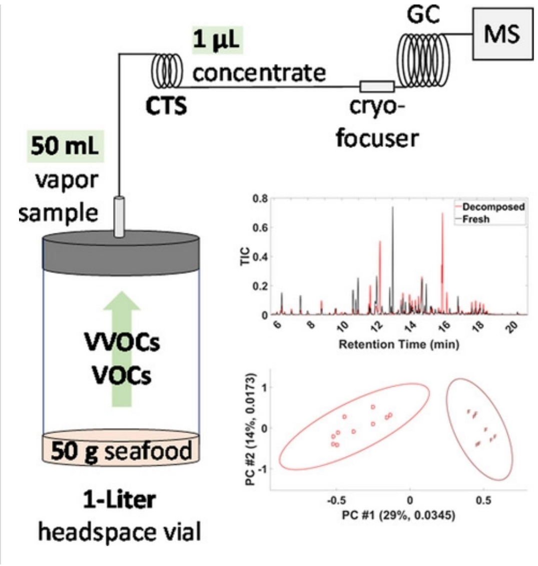
Large volume headspace GC/MS analysis for the identification of volatile compounds relating to seafood decomposition

Zhengfang Wang, Lowri S. de Jager, Timothy Begley, Susan Genualdi

Pages: 1195-1210 | First Published: 22 January 2022

Large volume headspace GC/MS generated analytical results that can be directly compared to sensory evaluation. Classification of fresh and decomposed seafood samples was successful. VOCs relating to seafood decomposition were identified.



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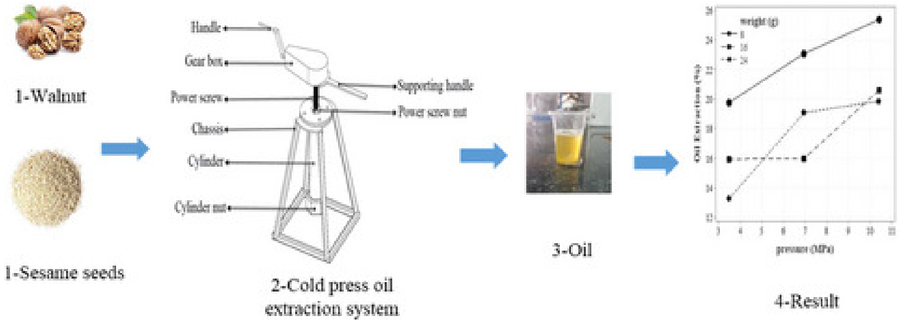
Modeling for extraction of oil from walnut and sesame using batch flow cold press oil extraction system

Pedram Ghiasi, Omid Sohrabi, Edris Rahmati, Gholamhassan Najafi, Mazlan Mohamed, Azim Ghasemnezhad

Pages: 1211-1221 | First Published: 22 February 2022



A new cold press oil extraction system was employed for extracting the oil from oilseeds (walnut and sesame) in the low volume. Sample mass (g), applied pressure (MPa), and processing temperature of oil (°C) were selected as independent variables. Response surface methodology was employed for statistical analysis and data optimization. Optimal level of independent variables for walnut and sesame were 8.03 g, 10.41 MPa, and 27.37°C; 20 g, 13.88 MPa, and 27°C, respectively.

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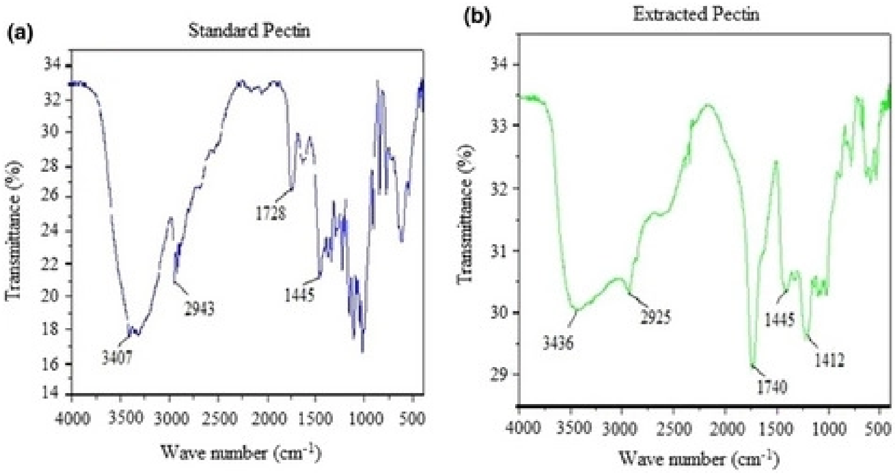
Optimization and characterization of pectin extracted from banana and papaya mixed peels using response surface methodology

Tanje Mada, Ramesh Duraisamy, Fisseha Guesh

Pages: 1222-1238 | First Published: 23 January 2022



The current study focused on the extraction and optimization of pectin from banana–papaya mixed peel wastes. The extraction conditions were optimized by the analysis of variance (ANOVA) and response surface methodology (RSM) approach. The physicochemical and functional properties of the obtained pectin were also evaluated.

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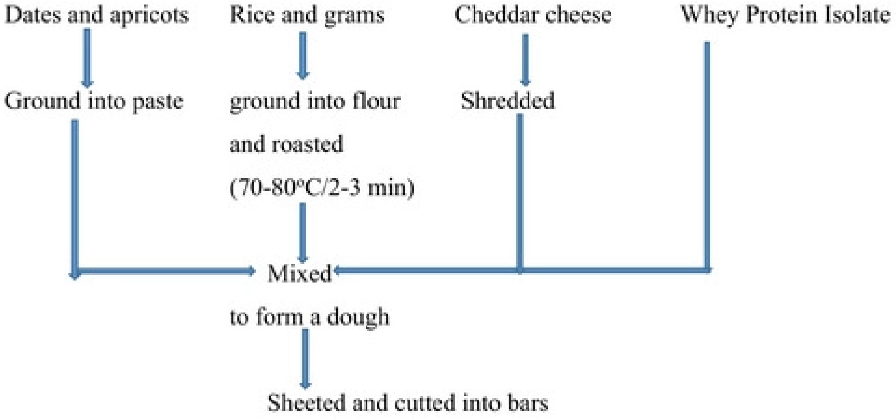
Development of energy-rich protein bars and in vitro determination of angiotensin I-converting enzyme inhibitory antihypertensive activities

Sidra Jabeen, Faiqa Javed, Navam S. Hettiarachchy, Amna Sahar, Aysha Sameen, Moazzam Rafiq Khan, Azhari Siddeeg, Ayesha Riaz, Rana Muhammad Aadil

Pages: 1239-1247 | First Published: 23 January 2022



These bars were studied for the compositional analysis (moisture, protein, and lipid content), protein characterization through sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE), and in vitro determination of the angiotensin I-converting enzyme (ACE-I) antihypertensive activity. Moisture and lipid content in bars were 22% and 0.057%–0.313%, respectively, while protein contents varied from 22.3% to 23.6%. Electrophoresis analysis of proteins in bar # 1 (cheese +WPI) showed the four bands at 62, 24, 20, and 12 kDa. Bar #2 (10% roasted chickpea flour) showed some additional bands at 40, 36, 34, and 28 kDa while relatively lower antihypertensive activity than bars #1 and 3.

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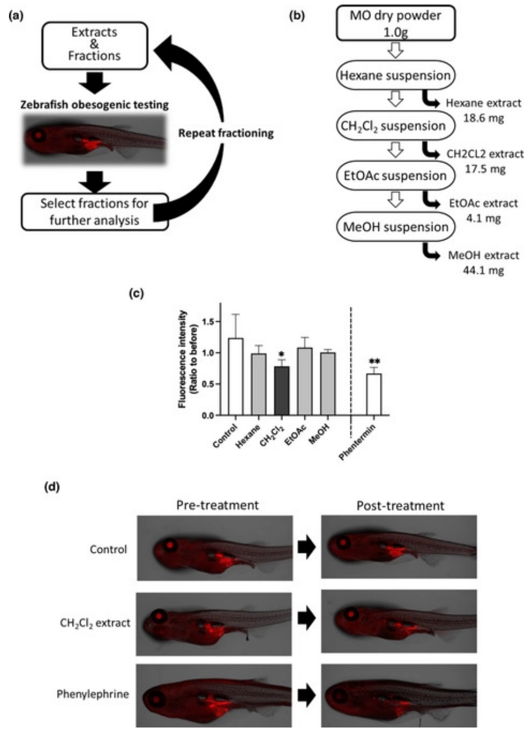
Zebrafish obesogenic test identifies anti-adipogenic fraction in *Moringa oreifera* leaf extracts

Izumi Matsuoka, Kanae Hata, Hirotaka Katsuzaki, Hiroko Nakayama, Liqing Zang, Mizuho Ota, Youngil Kim, Djong-Chi Chu, Lekh Raj Juneja, Norihiro Nishimura, Yasuhito Shimada

Pages: 1248-1256 | First Published: 11 February 2022



We performed zebrafish obesogenic test to identify anti-adipogenic fraction in Moringa oleifera leaf. Phenotype-driven zebrafish screening can be a reasonable strategy for identifying bioactive components in natural products. Using zebrafish obesogenic test, we identified that the dichloromethane extract of *Moringa oleifera* leaf and its subfraction (Fr. 2) reduced VAT accumulation in young zebrafish. In the zebrafish VAT, expression of early adipogenesis markers, *cebpb* and *cebpd*, was significantly ($p < .05$) decreased by Fr. 2, as was the expression of the late differentiation marker *cebpa*. We also confirmed that the subfractions of Fr. 2 also suppressed adipogenesis in ZOT and mouse 3T3-L1 preadipocytes.

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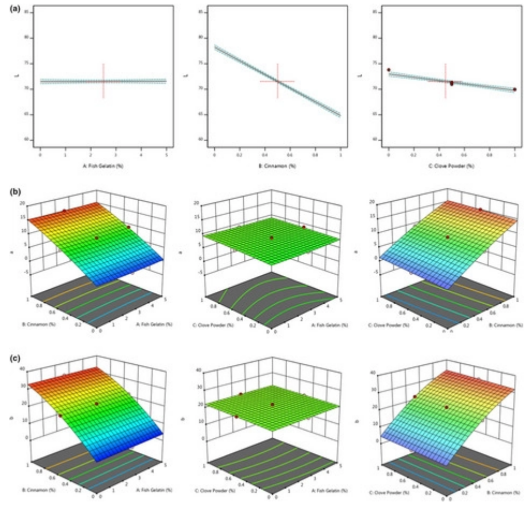
Response surface optimization of pudding formulation containing fish gelatin and clove (*Syzygium aromaticum*) and cinnamon (*Cinnamomum verum*) powder: Effect on color, physicochemical, and sensory attributes of the final pudding product

Nasrin Choobkar, Amir Daraei Garmakhany, Abdolraza R. Aghajani, Maryam Ataee

Pages: 1257-1274 | First Published: 26 February 2022



In this study, the pudding formulation was optimized regarding the fish/cow gelatin ratio, cinnamon and clove powder, and physicochemical as well as sensory analysis. The optimal FG/BG and cinnamon and clove powder were introduced 1.479, 0.288, and 0.619%, respectively.

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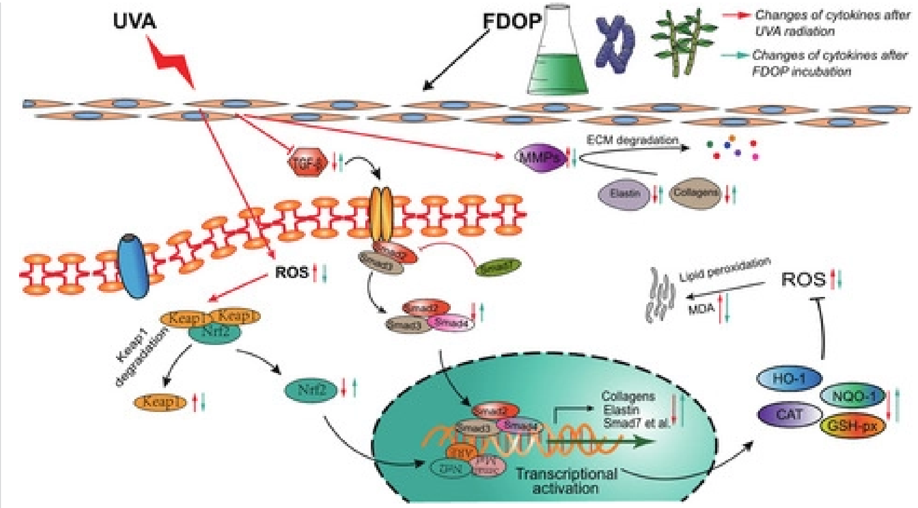
Fermented *Dendrobium officinale* polysaccharides protect UVA-induced photoaging of human skin fibroblasts

Yongtao Zhang, Shiquan You, Dongdong Wang, Dan Zhao, Jiachan Zhang, Quan An, Meng Li, Changtao Wang

Pages: 1275-1288 | First Published: 07 February 2022



The regulation of human skin fibroblast (HSF) protection mechanism explored by fermented *Dendrobium officinale* polysaccharides (FDOP) in this experiment is roughly shown in Figure 7. It is through stimulating the conduction of Nf-E2-related factor 2/Kelch-like ECH-associated protein 1 (Nrf2/Keap1) and transforming growth factor-β (TGF-β)/Smads signaling pathways to upregulate the expression of downstream target genes.

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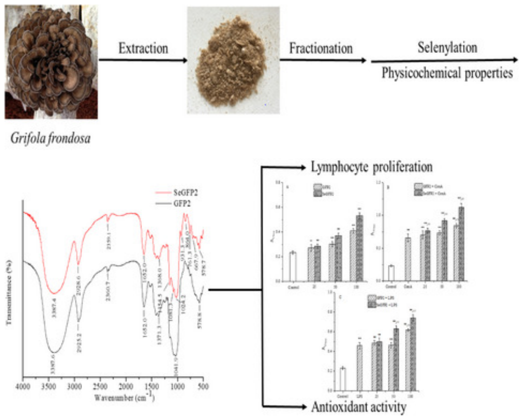
Immunostimulatory and antioxidant activities of the selenized polysaccharide from edible *Grifola frondosa*

Qian Li, Linfei Zhu, Xingpu Qi, Ting Zhou, Yonglian Li, Mingjie Cai, Yuting Yan, Jian-Ya Qian, Daxin Peng

Pages: 1289-1298 | First Published: 02 February 2022



A novel selenized polysaccharide (SeGFP2) from *G. frondosa* was prepared. Structural features were elucidated by GC-MS, methylation, HPSEC-MALLS-RI, etc. SeGFP2 with low molecule mass exhibited stronger immunostimulatory ability. A selenized *G. frondosa* polysaccharide, SeGFP2, was modified in selenylation by nitric acid–sodium selenite (HNO3-Na2SeO3) method. Structural features were investigated, and the lymphocyte proliferation and antioxidant activities were compared taking GFP2 as control.

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Identification of the promising olive (*Olea europaea* L.) cultivars based on morphological and pomological characters

Ali Khadivi, Farhad Mirheidari, Younes Moradi, Simin Paryan

Pages: 1299-1311 | First Published: 07 February 2022

The present research demonstrates that local olive cultivars have unique characteristics that differentiate them from imported cultivars. These sets of data were used to identify unique and desirable cultivars morphologically. Thus, local cultivars provide novel genetic resources that should be conserved.

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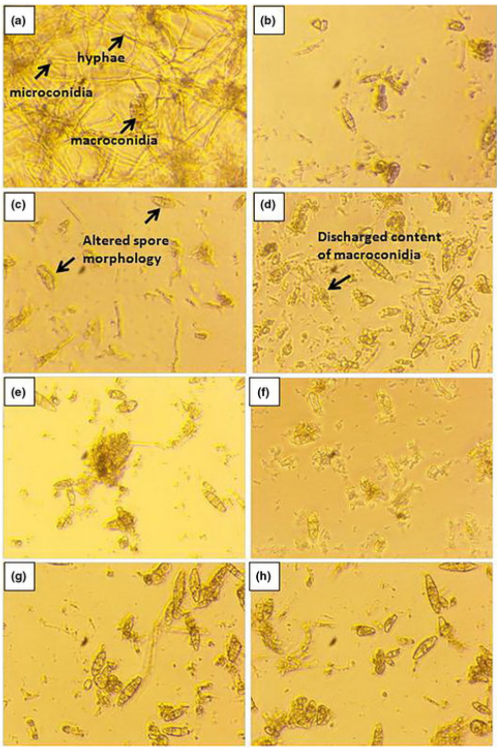
Tamjanika, a Balkan native variety of *Vitis vinifera* L.: Chemical characterization, antibacterial, and anti-dermatomycosis potential of seed oil

Nikoleta Đorđevski, Dejan Stojković, Jelena Živković, Dejan Pljevljakušić, Elizabeta Ristanović, Biljana Nikolić, Ana Ćirić

Pages: 1312-1319 | First Published: 11 February 2022



This study was designed to explore functional food properties of edible fatty oil obtained from Tamjanika seeds—autochthonous grape variety of Balkan Peninsula.

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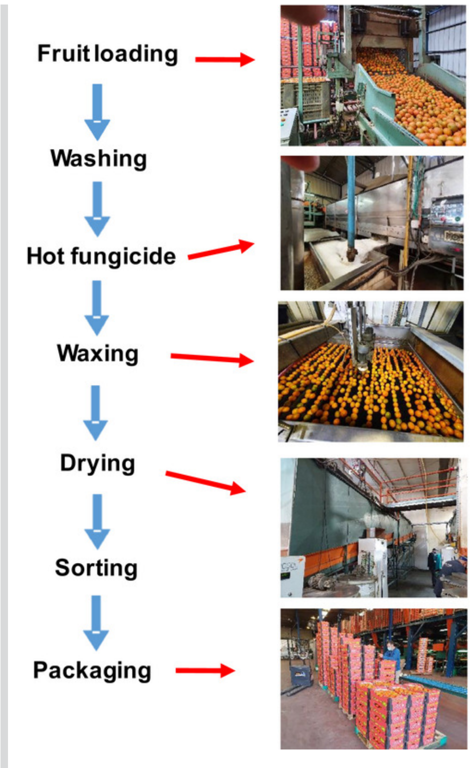
Effects of packinghouse operations on the flavor of ‘Orri’ mandarins

James Otieno, Abiola Owoyemi, Livnat Goldenberg, Yossi Yaniv, Nir Carmi, Ron Porat

Pages: 1320-1328 | First Published: 11 March 2022



The goal of this study was to examine the effects of commercial packinghouse operations, including the application of hot fungicides, waxing, and drying, on the flavor of ‘Orri’ mandarins. The key finding is that commercial waxing significantly increased ethanol and ethyl ester volatile levels, and somewhat harmed fruit-flavor acceptability and increased off-flavor sensations.

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ERRATUM

Open Access

Erratum to Nutritional evaluation of complementary porridge formulated from orange-fleshed sweet potato, amaranth grain, pumpkin seed, and soybean flours

Pages: 1329 | First Published: 04 March 2022

This article corrects the following: >

Nutritional evaluation of complementary porridge formulated from orange-fleshed sweet potato, amaranth grain, pumpkin seed, and soybean flours

Mary R. Marcel, James S. Chacha, Chigozie E. Ofoedu

Volume 10 , Issue 2 , Food Science & Nutrition | pages: 536-553 | First Published online: December 16, 2021

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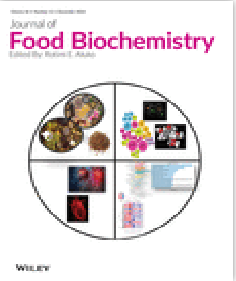

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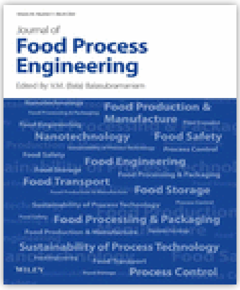

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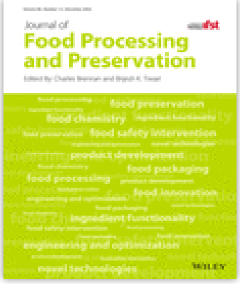

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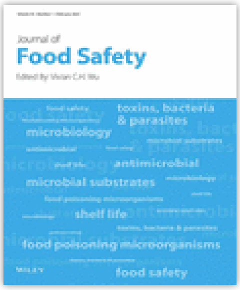

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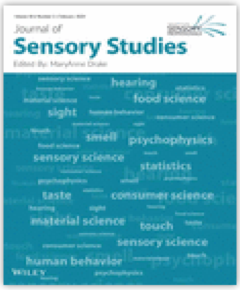

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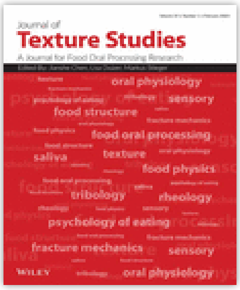

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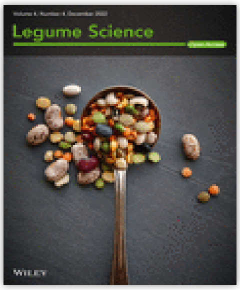

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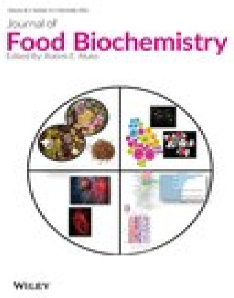

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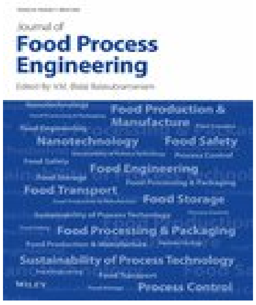

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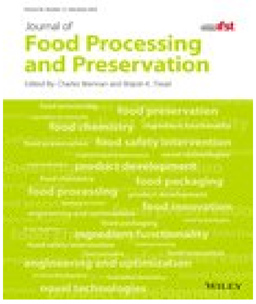

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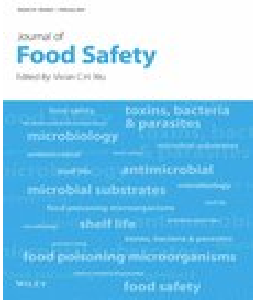

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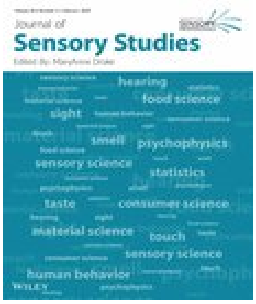

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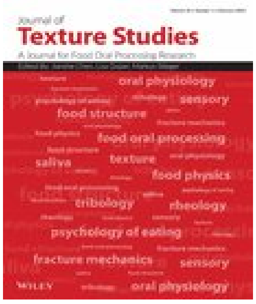

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REVIEW

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Does propolis have any effect on rheumatoid arthritis? A review study

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which inflammation and oxidative stress play a key role in its pathophysiology. Complementary therapies along with medications may be effective in the control of RA. Propolis is a natural substance extracted from beehives, which have confirmed anti-inflammatory and antioxidant effects. The present study aimed to review the possible effects of propolis on inflammation, oxidative stress, and lipid profile in patients with RA. English articles in online databases such as PubMed-Medline, AMED, Google Scholar, EMBASE, Scopus, and Web of Science databases were searched. Pieces of evidence show that supplementation with propolis may have therapeutic effects on RA patients. Due to increased inflammation and oxidative stress in the affected joints of RA patients, propolis could inhibit the inflammatory cascades by inhibiting the nuclear factor kappa B pathway and reducing reactive oxygen species, malondialdehyde, and interleukin-17 by increasing some antioxidants. Therefore, inflammation and pain reduce, helping improve and control RA in patients. Further investigations are required with larger sample sizes and different doses of propolis to demonstrate the definite effects of propolis on various aspects of RA.

KEYWORDS
inflammation, oxidative stress, propolis, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a heterogeneous autoimmune and systemic disorder in which cytokines and inflammatory responses play a key role in its pathogenesis (Lubberts & van den Berg, 2013; Nattagh-Eshtivani et al., 2021). Chronic inflammation starts in the synovial membrane and develops into subsequent lesions in the joint cartilage (Lubberts & van den Berg, 2013). The prevalence of RA is estimated at 0.5%–1.0% in the adult population worldwide (Vaghef-Mehrabany et al., 2016). The risk of mortality is higher in patients with RA than in the general population (Helli et al., 2016). Evidence suggests that the higher mortality rate of RA patients is due to the increased cardiovascular risk (Myasoedova & Gabriel, 2010).

Despite the extensive research that has unveiled some of the contributing factors to the initiation and development of RA, the exact etiology of the disease remains unknown (Tobón et al., 2010). Oxidative stress and inflammation may be significantly involved in the physiopathology of RA, and evidence attests to the increased level of oxidative stress biomarkers and decreased blood antioxidants in patients with RA (Filippin et al., 2008; Kalpakcioglu & Şenel, 2008; Kamanlı et al., 2004; Taysi et al., 2002). Furthermore, it is proposed that reactive oxygen species (ROS) could cause inflammatory responses in RA by activating nuclear factor kappa B (NF-κB) (Filippin et al., 2008). Therefore, using antioxidant supplements may help reduce the symptoms and improve the quality of life in RA patients.

The treatment of RA patients with nonsteroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs could ameliorate the symptoms, although the patients may experience complications such as osteoporosis, diabetes mellitus, and weight gain; these treatments are also rather expensive (Gautam & Jachak, 2009; Mousa et al., 2021; O'Dell, 2004). Therefore, complementary treatments have attracted the attention of researchers to reduce the complications and costs of RA treatment. Studies regarding herbal medicines have confirmed the beneficial effects of medicinal plants on the prevention and management of chronic diseases such as RA (Ernst, 2010; Kaur et al., 2012; Sarker et al., 2020).

Propolis (bee glue) is a resinous substance that honeybees collect from various plants and mix with wax and other secretions for the construction and protection of beehives (Barlak et al., 2011; Cardoso et al., 2011; Pascoal et al., 2014; Sforcin & Bankova, 2011). Propolis contains more than 300 chemical compounds, such as flavonoids (flavones, flavanones, flavonols, and dihydroflavonols), fatty acids, phenolic acids, aliphatic and aromatic acids, steroids, amino acids, polyphenolic acids, alcohols, terpenes, sugars, and esters (Bankova, 2005; Barlak et al., 2011; Nattagh-Eshtivani et al., 2021). The numerous biological and pharmacological properties of propolis have also been confirmed, including antimicrobial (Scazzocchio et al., 2006; Uzel et al., 2005), antiviral (Kujumgiev et al., 1999), antifungal (Kujumgiev et al., 1999), free radical-scavenging (Ichikawa et al., 2002; Scheller et al., 1990), anti-inflammatory (Boufadi et al., 2021), hepatoprotective, anticancer, antioxidant (Russo et al., 2002), antineurodegenerative, and immune system-stimulating properties (Farooqui & Farooqui, 2012; Sforcin, 2007). Moreover, propolis has been reported to positively influence cartilage, bones, and dental pulp regeneration (Ramos & Miranda, 2007). The aim of this study was to review the previous publications on the anti-inflammatory, antioxidant, and cardioprotective effects and also its possible mechanisms related to propolis supplementation in RA disease.

2 | METHODS

A systematic search was carried out in the PubMed-Medline, AMED, Google Scholar, EMBASE, Scopus, and Web of Science databases by two independent reviewers (M. M. and H. B.) to identify the relevant articles. The key terms, including "propolis," in combination with "inflammation," "oxidative stress," "antioxidant," "anti-inflammatory," "dyslipidemia," "lipid profile," "cardiovascular disease," "heart disease," "atherosclerosis," and "inflammatory markers," were used for an electronic search strategy. After checking the titles and abstracts of the resulting articles, all the relevant studies published only in English were reviewed subsequently; the eligible animal and clinical trials studies were selected, and duplicate citations were then removed.

2.1 | The effects of propolis supplementation on inflammation in RA

Ample evidence suggests that systemic inflammation plays a key role in the development and progression of several chronic diseases, including RA (Balkarli et al., 2016; Laveti et al., 2013). As such, diminishing inflammation may be associated with the reduced risk of RA. In addition, environmental factors have been shown to induce immune cell responses, causing the immune system to release large amounts of pro-inflammatory cytokines (Fox, 2005). Among these cytokines, tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) could cause joint degradation by inducing inflammation and synovial cell activation (Furst et al., 2003; Weinblatt et al., 1999; Yaykasli, 2013).

Inflammatory cascades are responsible for the overexpression of TNF-α. This cytokine leads to synovitis, articular damage, and overproduction of other cytokines, particularly IL-6, which increases inflammation and joint degeneration (Scott et al., 2010). Interleukin-17 (IL-17) is another pro-inflammatory cytokine, the catabolic effects of which are mediated by its ability to stimulate cartilage and bone degradation (Figure 1) (Koenders et al., 2005; Van Den Berg & Miossec, 2009). Therefore, these cytokines are often targeted in the treatment of RA patients, and researchers have attempted to effectively prevent and manage the inflammatory cascade by using dietary supplements, which have fewer side effects and are cost-efficient.

Propolis as a complementary medicine has been used in the treatment of various diseases (Farooqui & Farooqui, 2012; Fukuda et al., 2015; Hu et al., 2005; Santos, 2012), and investigations in this regard have confirmed that propolis and its flavones could cause reduction in inflammation (Afsharpour et al., 2017; De Almeida & Menezes, 2002; Jalali et al., 2020). Furthermore, several studies have been conducted on animal models (Table 1). Fang et al. (2013) reported that 160 mg/kg/day of the ethanol extract of propolis (EEP) could significantly decrease IL-6 in mice after 14 weeks of treatment. In another study, Corrêa et al. observed that 100 mg/kg/day of Brazilian red propolis reduced the IL-6 and TNF-α levels in mice after 9 days of administration (Corrêa et al., 2017). The findings of Kismet et al. also demonstrated that the intraperitoneal daily dosage of propolis (200 mg/kg) could significantly decrease TNF-α and IL-6 in rats with nonalcoholic fatty liver disease after 2 weeks of treatment (Kismet et al., 2017). In another study, the administration of propolis by gavage (500 mg/kg/day) for 4 days has shown reduction in the intraperitoneal permeability of mice by lowering the effects of inflammatory factors (Lima et al., 2014).

According to the study by Chen et al., propolis gavage (919.5 mg/kg/day) could decrease serum TNF-α, IL-1β, and IL-6, whereas a lower dose (183.9 mg/kg/day) induced moderate responses in terms of TNF-α and IL-1β levels (Chen et al., 2018). Furthermore, Cheung K. W. et al. reported that Brazilian propolis and its components (artepillin C) inhibited IL-17 production in human CD4 T cells (Cheung et al., 2011). Therefore, it could be concluded that propolis has antiarthritic effects as T-helper 17 cells, which are involved in the pathogenesis of RA (Iwakura & Ishigame, 2006; Steinman, 2007). Therefore, it is suggested that propolis supplementation in patients with RA could control the disease by decreasing the inflammatory cascade and the secretion of pro-inflammatory indices. Tables 1 and 2 summarize the animal studies and clinical trials regarding the anti-inflammatory effects of propolis, respectively.

2.2 | Anti-inflammatory mechanism of propolis

During the inflammation process, macrophages activate and release pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6. These

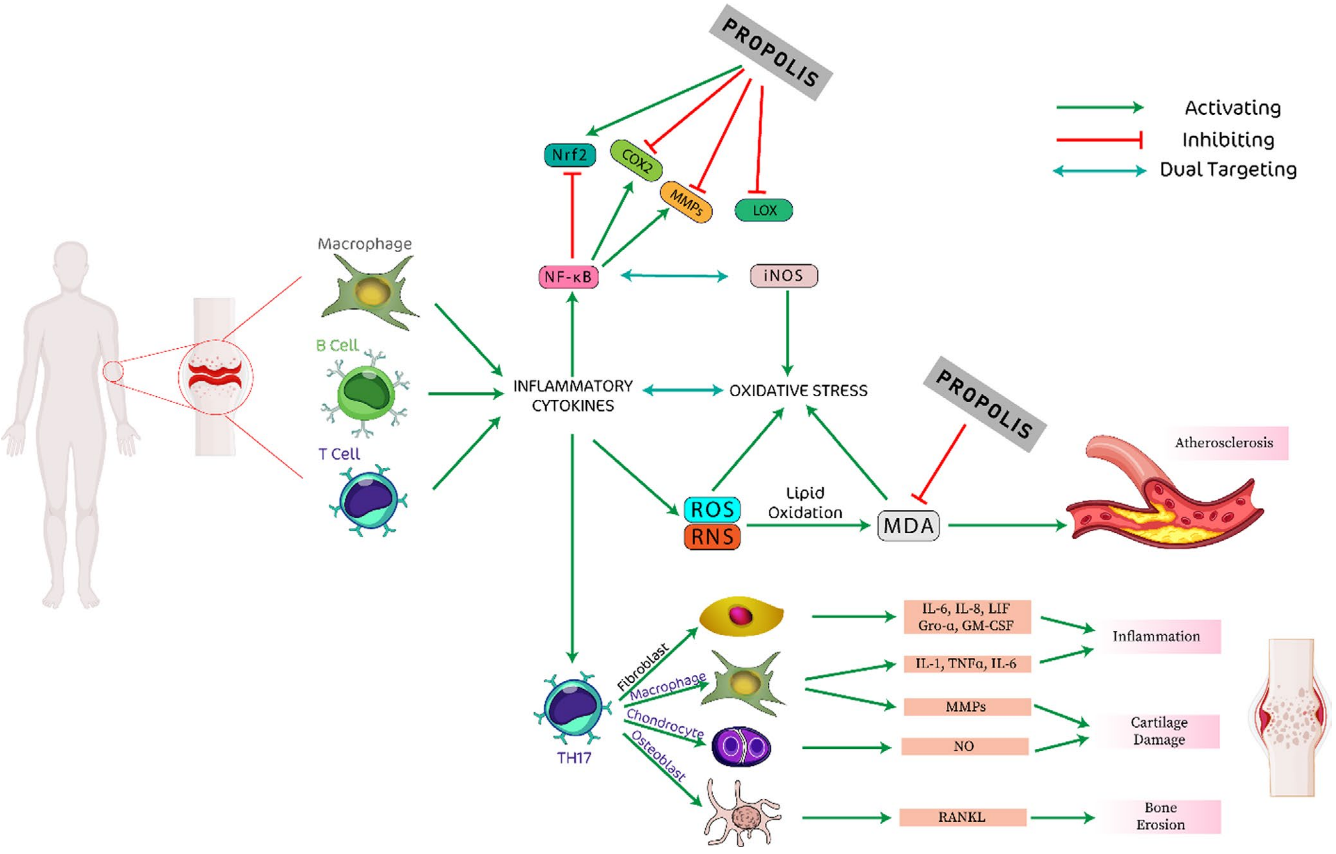

FIGURE 1 Hypothetical mechanism of effects of propolis on reduction of inflammation, oxidative stress, and atherosclerosis

TABLE 1 Summary of animal studies on anti-inflammatory effects of propolis

First author (year)	Country	Subjects	Administered dose of propolis	Duration (day)	Outcomes	Reference
Hu et al. (2005)	China	Mice	1 ml/100 g	–	↓ IL-6	Hu et al. (2005)
Machado et al. (2012)	Brazil	Mice	5 mg/kg/day	6	↓ IL-6 and TNF-α levels	Machado et al. (2012)
Fang et al (2013)	China	Mice	160 mg/kg/day	98	↓ IL-6	Fang et al. (2013)
Hemieda et al. (2015)	Egypt	Rat	50/100 mg/kg/day	42	↓ CRP, TGF-β	Hemieda et al. (2015)
Elissa et al. (2015)	Egypt	Rat	0.6 g/kg/day	21	↓ TNF-α	Elissa et al. (2015)
Corrêa et al. (2017)	Brazil	Mice	100 mg/kg/day	9	↓ IL-6 and TNF-α levels	Corrêa et al. (2017)
Wang et al. (2018)	China	Rat	300 mg/kg/day	7	Colonic inflammatory markers IL-1β, IL-6 suppressed by propolis	Wang et al. (2018)
Kismet et al. (2017)	Turkey	Rat	200 mg/kg	14	↓ TNF-α and IL-6 levels	Kismet et al. (2017)
El Rabey et al. (2017)	Saudi Arabia	Rat	20% w/w	28	↓ IL-6	El Rabey et al. (2017)
Chen et al. (2018)	Taiwan	Rat	919.5 mg/kg/day	56	↓ TNF-α, IL-1β, and IL-6	Chen et al. (2018)

Abbreviations: ↑, increase; ↓, decrease; ↔, no effect; CRP, C-reactive protein; IL, interleukin; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor-alpha.

TABLE 2 Summary of clinical trials on anti-inflammatory effects of propolis

First author (year)	Country	Sample size (T/C)	Subjects	Type and dose of propolis	Duration (week)	Outcomes	Reference
Zhao et al. (2016)	China	32/33	T$_2$DM	900 mg/day	18	↓ TNF-α ↑ IL-6	Zhao et al. (2016)
Khayyal et al. (2002)	Egypt	22/24	Patients with mild-to-moderate asthma	2 ml/day	8	↓ TNF-α, IL-6, and IL-8 ↑ IL-10	Khayyal et al. (2002)
Fukuda et al. (2015)	Japan	41/39	T$_2$DM	226.8 mg/day	8	↔ CRP, ↔ TNF-α and IL-6	Fukuda et al. (2015)
Gao et al. (2018)	China	25/30	T$_2$DM	900 mg/day	18	↑ IL-6	Gao et al. (2018)
Mujica et al. (2017)	Chile	35/32	Healthy subjects	–	12	↔ CRP	Mujica et al. (2017)
Afsharpour et al. (2017)	Iran	30/30	T$_2$DM	1500 mg/day	8	↓ CRP and TNF-α	Afsharpour et al. (2017)
Zhu et al. (2018)	China	30/30	Elderly subjects	66 mg/day	96	↓ IL-6	Zhu et al. (2018)
Zakerkish et al. (2019)	Iran	50/44	T$_2$DM	1000 mg/day	12	↓ CRP and TNF-α ↔ IL-6	Zakerkish et al. (2019)
Gholaminejad et al. (2019)	Iran	29/28	Men with asthenozoospermia	1500 mg/day	10	↓ CRP and TNF-α	Gholaminejad et al. (2019)
Darvishi et al. (2020)	Iran	26/24	Patients with breast cancer	500 mg/day	12	↔ TNF-α	Darvishi et al. (2020)
Soleimani et al. (2021)	Iran	24/25	Healthy subjects	900 mg/day	4	↓ IL 6	Soleimani et al. (2021)

Abbreviations: ↑, Increase; ↓, decrease; ↔, no effect; C, control; CRP, C-reactive protein; IL, interleukin; T, treatment; T$_2$DM, type II diabetes mellitus; TNF-α, tumor necrosis factor-alpha.

activated macrophages induce the translocation of NF-κB. NF-κB activation plays a pivotal role in the production and stimulation of various cytokines and inflammatory mediators (TNF-α, IL-1, IL-2, IL-6, and IL-8) while also participating in the regulation of inflammation (Baeuerle, 1991; Surh et al., 2001). Furthermore, NF-κB is critically involved in modulating the survival, differentiation, and activation of immune cells (Liu et al., 2017). The NF-κB signaling pathway also partakes in the production of nitric oxide (NO) by stimulating inducible nitric oxide synthase (iNOS), which is an inflammatory mediator (Pahlavani et al., 2019; Xie et al., 1994).

Propolis has potent anti-inflammatory activities (Ying-Hua et al., 2012). It reduces the gene expression of iNOS, the cytokines mediated by NF-κB activation, and the immune response in T cells (Banskota et al., 2001; Paulino et al., 2008). Also as demonstrated in previous research, propolis components could have directly regulated the basic immune cell functions (Wolska et al., 2019). For example, in lipopolysaccharide-stimulated RAW264.7 macrophages, neovestitol, an isoflavonoid derived from propolis, showed an immunological modulatory impact by inhibiting NO production and lowering pro-inflammatory cytokine levels (Bueno-Silva et al., 2017). Propolis extracts and propolis compounds (caffeic acid, phenethyl ester, quercetin, and hesperidin) could suppress DNA synthesis and the production of inflammatory cytokines (IL-1, IL-12, IL-2, and IL-4) in Th1- and Th2-type T cells while enhancing the production of transforming growth factor-β1 (TGF-β1) (Ansorge et al., 2003). Furthermore, the suppression of macrophage activation and differentiation has been proposed as one of the possible mechanisms causing propolis' anti-inflammatory and immunological benefits (Araujo et al., 2012).

Caffeic acid phenethyl ester (CAPE) is an important component of propolis with anti-inflammatory properties (Tolba et al., 2013). Evidence suggests that CAPE is a potent modulator of arachidonic acid (AA) that blocks the release of AA from the cell membrane, thereby suppressing the gene expression of lipoxygenase and cyclooxygenase (COX) enzymes (Mirzoeva & Calder, 1996). According to various investigations, CAPE is a dominant and selective inhibitor of NF-κB activation; CAPE has been shown to inhibit NF-κB activation precisely and completely by a wide range of inflammatory stimuli, including TNF-α and H_2O_2 (Ramos & Miranda, 2007).

Propolis also prevents the production of leukotriene and prostaglandin. Propolis flavonoids may be responsible for their effects on the COX enzyme, which has been reported to suppress prostaglandin-endoperoxide synthase (Mirzoeva & Calder, 1996). In this regard, Woo et al. examined the effects of chrysin on the expression of COX-2, reporting that chrysin could significantly suppress the expression of COX-2 protein and mRNA (Woo et al., 2005). In an in vitro study by Kao et al., the anti-inflammatory effects of artepillin C were investigated on mice, and the obtained results indicated that artepillin C inhibited prostaglandin E2 synthesis and NO production while also reducing NF-κB activity in mice (Kao et al., 2010).

Notably, the anti-inflammatory effects of quercetin have been attributed to the downregulation of the extracellular signal-regulated kinase, p38, Akt, Janus kinase-1, tyrosine kinase 2 (TYK2), signal transducer, and NF-κB activator. This compound has also been shown to scavenge free radicals (Kao et al., 2010). Furthermore, a large number of other flavonoids such as apigenin, galangin, and pinocembrin are found in propolis. Zhang et al. reported that apigenin reduced the mRNA levels of IL-1, IL-6, and TNF-α in human THP-1-derived macrophages (Zhang et al., 2014). In addition, pinocembrin significantly reduced the levels of these pro-inflammatory cytokines in RAW 264.7 macrophage cells, whereas it significantly increased the levels of IL-10 (Soromou et al., 2012). Galangin significantly lowered the levels of IL-6 and TNF-α cytokines in the same RAW 264.7 cell line (Lee et al., 2018). In vivo, oral administration of propolis in C57BL/6 mice for 14 days inhibited spleen cell production of IL-1, IL-6, IL-2, IL-10, and IFN-γ (Missima et al., 2010). Moreover, an ethanolic extract of Brazilian propolis inhibited the expression of IL-17 in mice with collagen-induced arthritis (Tanaka et al., 2012). Another study found that the anti-inflammatory activity of Brazilian green propolis in stimulated J774A.1 macrophages is mediated through the inhibition of NO and pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 (Szliszka et al., 2013). As a result, propolis and its ingredients might exert potential natural anti-inflammatory agents that work by modifying immune responses.

2.3 | Effects of propolis in relation to oxidative stress in RA

Although the exact etiology of RA remains unknown, several studies have confirmed the role of ROS in the pathophysiology of the disease (Bauerova & Bezek, 2000). ROS are naturally produced during aerobic metabolism, and the cells are protected against ROS by the antioxidant defense system (Roy et al., 2017). When ROS production exceeds the capacity of the antioxidant system, oxidative stress occurs and causes metabolic dysfunction and extensive damage to fats, proteins, and DNA. Ultimately, the free radicals produced from oxygen metabolism destroy the antioxidant system (Tao et al., 2018).

In RA, the activation of neutrophils and macrophages (main cells of inflammatory synovial fluid) increases the production of ROS, which are important mediators of tissue damage in arthritis (Kamanlı et al., 2004; Oztürk et al., 1999). On the contrary, malondialdehyde (MDA) is the main indicator of lipid peroxidation, which increases in synovial fluid of RA patients. Previous findings have suggested that MDA increases in the serum, plasma, and synovial fluid in RA under normal conditions (Das et al., 2020). Studies have also shown that serum antioxidants are lower in RA patients than in healthy individuals, and the activity of antioxidant enzymes such as glutathione peroxidase (GPX), superoxide dismutase (SOD), and catalase (CAT) is altered in the serum of these patients. However, contradictory results have been proposed in this regard (Akyol et al., 2001; Kiziltunc et al., 1998; Sarban et al., 2005).

In addition to acting as a protective mechanism against ROS, antioxidants could suppress the expression of the cytokines and collagenase induced by TNF-α, which is also a protective mechanism against arthritis (Halliwell et al., 1988; Sato et al., 1996). It is hypothesized that natural compounds with antioxidant properties may exert protective effects against RA (Bae et al., 2003; Wang et al., 2019). Propolis is a natural compound that is expected to be effective in reducing oxidative stress levels (Abass et al., 2017; Mujica et al., 2017; Pahlavani et al., 2020). Several studies have demonstrated that propolis could also decrease oxidative stress-related markers (MDA) and increase free radical scavenging enzymes (SOD and GPX) and the total antioxidant capacity (TAC) (Afsharpour et al., 2019; Jasprica et al., 2007). Table 3 presents the summary of the animal studies investigating the effects of propolis on oxidative stress.

TABLE 3 Summary of animal studies on the effects of propolis on oxidative stress

First author (year)	Country	Animal species	Propolis dosage	Duration (day)	Outcomes	Reference
Remirez et al. (1997)	Cuba	Rat	25, 50, and 100 mg/kg/day	–	↓ MDA in liver	Remirez et al. (1997)
Chopra et al. (1995)	India	Rat	50 and 100 mg/kg/day	–	↓ MDA	Chopra et al. (1995)
Rodriguez et al. (1996)	Cuba	Rat	10, 50, and 100 mg/kg/day	–	↓ MDA	Rodriguez et al. (1997)
Ilhan et al. (1999)	Turkey	Rabbit	10 μmol/kg/day	–	↓ MDA	Ilhan et al. (1999)
Ozyurt et al. (2001)	Turkey	Rat	10 μmol/kg/day	–	↓ MDA	Ozyurt et al. (2001)
Shinohara et al. (2002)	Japan	Rat	–	–	↓ LPO	Shinohara et al. (2002)
Shukla et al. (2004)	India	Rat	200 mg/kg/day	–	↓ LPO ↑ Hepatic GSH level	Shukla et al. (2004)
Hu et al. (2005)	China	Rat	1 ml/100 g	56	↓ Fructose amine and MDA ↑ SOD	Hu et al. (2005)
Tan-no et al. (2006)	Japan	Mice	At dilutions of 1:100 and 1:1000	–	↓ NO production	Tan-no et al. (2006)
Sobocanec et al. (2006)	Croatia	Mice	100 mg/kg/day	–	↑ CAT and SOD ↓ TBARS	Sobocanec et al. (2006)
Eraslan et al. (2007)	Turkey	Rat	200 mg/kg/day	7 and 21	↔ Antioxidant enzymes and MDA levels	Eraslan et al. (2007)
Nirala and Bhadauria (2007)	India	Rat	100 and 200 mg/kg/day	–	GSH was restored by propolis treatment	Nirala and Bhadauria (2008)
Kismet et al. (2008)	Turkey	Rat	100 mg/kg/day	7	↓ Plasma and liver levels of MDA ↑ Liver GPX activities	Kismet et al. (2008)
Kanbur et al. (2008)	Turkey	Rat	100 mg/kg/day	28	↓ MDA levels ↑ SOD, CAT, and GPX	Kanbur et al. (2009)
Alyane et al. (2008)	Algérie	Rat	100 mg/kg/day	4	↓ MDA formation and production of superoxide anion	Alyane et al. (2008)
Yousef et al. (2009)	Egypt	Rat	50 mg /kg/day	70	↓ TBARS ↑ GSH, CAT, and GST	Yousef et al. (2009)
Zhao et al. (2009)	China	Mice	200 mg/kg/day	3	Propolis inhibited lipid peroxidation and oxidized ↑ GSH	Zhao et al. (2009)
Abo-Salem et al. (2009)	Egypt	Rat	100, 200, and 300 mg/day	40	↓ MDA ↑ GSH and SOD activities	Abo-Salem et al. (2009)
El-Sayed et al. (2009)	Egypt	Rat	200 mg/kg/day	35	↓ MDA pancreatic content and serum NO ↑ Serum GSH and CAT activities ↑ Pancreatic SOD activities	El-Sayed et al. (2009)
Khalil et al. (2010)	Egypt	Rat	Dietary propolis powder (0.1% and 0.2%)	42	↓ MDA ↑ GSH, SOD, and CAT activities	Khalil and El-Sheikh (2010)
Nader et al. (2010)	Egypt	Rabbit	75 mg/kg/day	28	↓ TBARS ↑ GSH	Nader et al. (2010)
Seven et al. (2010)	Turkey	Broiler	1 g/kg/day	42	↓ MDA	Seven et al. (2010)
Zhu et al. (2010)	China	Rat	100 mg/kg/day	56	↓ MDA and NOS ↑ SOD and GPX	Zhu et al. (2011)
Bhadauria (2011)	India	Rat	200 mg/kg/day	14	↓ TBARS ↑ CAT and GSH	Bhadauria and Medicine (2012)
Zhu et al. (2011)	China	Rat	100 mg/kg/day	56	↓ Blood and renal MDA	Zhu, Chen, et al. (2011)

TABLE 3 (Continued)

First author (year)	Country	Animal species	Propolis dosage	Duration (day)	Outcomes	Reference
Garoui et al. (2011)	Tunisia	Rat	1 g propolis/100 g diet	–	Propolis ↑ activity of antioxidant enzymes (GPX, CAT, and SOD) and the level of GSH in the kidney	Garoui et al. (2012)
Yonar et al. (2011)	Turkey	Rainbow trout	50 mg/kg/day	14	↓ MDA ↑ SOD, GPX, GSH, and CAT	Yonar et al. (2011)
Attia et al. (2012)	Egypt	Rat	50 mg/kg/day	70	↑ CAT, SOD, and GPX ↓ LPO	Attia et al. (2012)
Oršolić et al. (2012)	Croatia	Mice	50 mg/kg/day	7	↓ MDA content in liver and kidney	Oršolić et al. (2012)
Gulhan et al. (2012)	Turkey	Rainbow trout	10, 20, and 30 PPM	96 hr	↓ MDA	Fuat Gulhan et al. (2012)
Selamoglu-Talas et al. (2013)	Turkey	Rat	200 mg/kg/day	5	↑ CAT activity ↓ MDA	Selamoglu-Talas et al. (2013)
El-Awady et al. (2013)	Egypt	Isolated rat aorta	400 μg/ml	3 hr	In vitro: ↑ SOD ↓ MDA	El-Awady et al. (2014)
Newairy et al. (2013)	Egypt	Rat	50 mg/kg/day	28	↓ TBARS ↑ CAT, SOD, and GSH	Newairy and Abdou (2013)
Su et al. (2014)	Taiwan	Hepatic stellate cells of rat	200 and 400 mg/kg/day	28	↓ MDA	Su et al. (2014)
Abou-Zeid et al. (2015)	Egypt	Chick	0, 125, 250, and 500 mg/kg/day	42	↓ MDA ↑ SOD, GPX, and CAT activity	Abou-Zeid et al. (2015)
Hemieda et al. (2015)	Egypt	Rat	50 or 100 mg/kg/day	42	↓ MDA ↑ GSH, SOD, CAT, and TAC	Hemieda et al. (2015)
Sameni et al. (2015)	Iran	Rat	100 and 200 mg/kg/day	42	↓ MDA ↑ The activity of SOD and GPX	Sameni et al. (2016)
Al-Hariri et al. (2015)	Saudi Arabia	Rat	0.3 g/kg/day	14	↓ TBARS	Al-Hariri et al. (2016)
Elissa et al. (2015)	Egypt	Rat	0.6 g/kg/day	21	↓ MDA ↑ GSH	Elissa et al. (2015)
Kismet et al. (2017)	Turkey	Rat	200 mg/kg/day	14	↑ Total thiol ↓ MDA	Kismet et al. (2017)
Arslan et al. (2016)	Turkey	Japanese quail	0.5, 1, and 1.5 g/kg/day	8–42	↓ MDA	Sur Arslan and Tatlı Seven (2017)
Gul Baykalir et al. (2016)	Turkey	Rat	100 mg/kg/day	–	↓ MDA ↑ GSH and CAT level	Baykalir et al. (2018)
Bazmandegan et al. (2017)	Iran	Mice	100 and 200 mg/kg	24 and 48 hr	↑ SOD and GPX activity ↓ LPO	Bazmandegan et al. (2017)
Gong et al. (2017)	China	Mice	10 μmol/kg/day	28	↓ MDA and NO ↑ SOD and CAT activities and GSH	Gong et al. (2017)
El Rabey et al. (2017)	Saudi Arabia	Rat	20% w/w	28	↓ MDA ↑ CAT, SOD, and GST	El Rabey et al. (2017)
Alm-Eldeen et al. (2017)	Egypt	Mice	0.2 mg/kg/day	14	↓ MDA ↑ GSH, CAT, and SOD	Alm-Eldeen et al. (2017)
Rivera-Yañez et al. (2018)	Mexico	Mice	300 mg/kg/day	15	↑ SOD, CAT, and GPX	Rivera-Yañez et al. (2018)
Udo Nna et al. (2018)	Malaysia	Rat	300 mg/kg/day	28	↑ SOD, CAT, GPX, GSH, GST, and GSR ↓ MDA	Nna et al. (2018)

(Continues)

TABLE 3 (Continued)

First author (year)	Country	Animal species	Propolis dosage	Duration (day)	Outcomes	Reference
Aydin et al. (2018)	Turkey	Rabbit	200 mg/kg/day	28	↓ MDA ↑ GPX and CAT	Aydin et al. (2018)
Chen et al. (2018)	Taiwan	Rats	183.9 and 919.5 mg/kg/day	56	↑ SOD and GPX ↓ TBARS	Chen et al. (2018)
Abdel-Rahman et al. (2019)	Egypt	Rat	50 and 100 mg/kg/day	–	↓ MDA ↑ SOD, CAT, GPX, and GSH	Abdel-Rahman et al. (2020)
Shi et al. (2019)	China	Rat	200 mg/kg/day	84	↓ ROS ↓ RNS	Shi et al. (2019)

Abbreviations: ↑, increase; ↓, decrease; ↔, no effect; C, control; CAT, catalase; GPX, glutathione peroxidase; GSH, glutathione; GSR, glutathione reductase; GST, glutathione *S*-transferases; LPO, lipid peroxidation; MDA, malondialdehyde; NO, nitric oxide; NOS, nitric oxide synthases; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; T, treatment; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances.

In a clinical trial conducted by Mujica et al. (2017), propolis supplementation (15 drops twice a day) was reported to decrease thiobarbituric acid reactive substances and increase plasma glutathione (GSH). However, other studies have not confirmed the significant effects of propolis on improving oxidative stress (Gao et al., 2018; Zhao et al., 2016). According to Ebeid et al. (2016), consuming propolis capsules (1200 mg/day) for 10 days before radiotherapy significantly decreased MDA and increased TAC during and 10 days after the treatment. Furthermore, Hesami et al. conducted a double-blind, randomized-controlled trial on 62 patients with type II diabetes, reporting that propolis supplementation (500 mg/kg; thrice a day) improved the antioxidant defense mechanisms after 8 weeks by increasing the CAT activity (Hesami et al., 2019). The overexpression of mitochondrial catalase has been shown to diminish the incidence of arteriosclerosis in mice while exerting protective effects against cardiovascular dysfunction and injuries in human subjects (Lei et al., 2016; Tehrani & Moosavi-Movahedi, 2018). In this regard, Gao et al. reported that after 18 weeks of consuming Chinese propolis, a significant increase was observed in the serum GSH, flavonoids, and polyphenols of patients with type II diabetes (Gao et al., 2018). Recently Soleimani et al. also observed that the administration of propolis (450 mg/kg twice daily) significantly increased the levels of GSH and TAC and decreased total oxidant status (TOS) and MDA after 4 weeks of intervention (Soleimani et al., 2021).

According to the literature, the main antioxidant mechanisms of propolis polyphenols may be associated with their scavenging effects on ROS, while nitrogen species and chelating metal ions may also be involved in the production of free radicals, reduction of xanthine oxidase reaction, and synergistic effects with other antioxidants (Kurek-Górecka et al., 2013; Mujica et al., 2017). It is known that phenolic compounds, such as those found in propolis, act as antioxidants by interrupting the chain reaction of lipids (Torel et al., 1986), blocking chemiluminescence processes (Georgetti et al., 2003), and scavenging ROS (Bors et al., 1990). The antioxidant and reductive capacity of propolis against ROS could be attributed to two main mechanisms, namely the capacity of CAPE in activating NrF2 transcription factor (a regulatory protein associated with antioxidant protection and improvement in antioxidant enzymes) and the phenolic acid and flavonoid contents of propolis (CAPE, quercetin, apigenin, *p*-coumaric acid, cinnamic acid, and *p*-vanillin), which neutralize free radicals and oxidant compounds (Ichikawa et al., 2002; Lee et al., 2010). Moreover, propolis has been shown to significantly enhance vitamin C levels in the plasma, kidney, stomach, small intestine, and colon (Seven et al., 2010). Propolis could be absorbed through the bloodstream and act as a hydrophilic antioxidant in the absorption of vitamin C (Seven et al., 2010). Figure 1 represents the hypothetical mechanism of the effects of propolis on the reduction of inflammation and oxidative stress.

2.4 | Cardioprotective effects of propolis in RA

Rheumatoid arthritis is an inflammatory disease associated with the increased risk of cardiovascular mortality and morbidity (Aviña-Zubieta et al., 2008; Gonzalez-Gay et al., 2005). However, the exact mechanism of the elevated risk of cardiovascular diseases (CVDs) in RA patients should be further explored. The increased risk of CVD in RA patients may be due to dyslipidemia. Several observational studies have demonstrated that RA is associated with negative effects on lipid profile (Boers et al., 2003; Park et al., 1999, 2002). Dyslipidemia causes atherosclerosis and CVD (Nelson, 2013; Tietge, 2014), whereas reduced serum cholesterol leads to a significantly lower risk of CVD (González-Gay & González-Juanatey, 2014; Stamler et al., 2000). Furthermore, inflammation in RA patients plays a pivotal role in disease progression (González-Gay & González-Juanatey, 2014). Scientific evidence suggests that chronic inflammation in patients with RA is associated with a higher risk of CVD (Gonzalez-Gay et al., 2007; Gonzalez-Gay et al., 2005). Inflammation causes oxidative changes, which influence the structure of high-density lipoprotein (HDL) and decrease apolipoprotein-A1 in RA patients (Charles-Schoeman et al., 2009). In addition, the levels of the antioxidant enzyme associated with HDL (paraoxonase-1) have been reported to be lower in patients with RA compared to healthy controls (Charles-Schoeman et al., 2012).

The cardioprotective effects of propolis have been confirmed in several studies (Ahmed et al., 2017; Alyane et al., 2008; Daleprane & Abdalla, 2013). The in vitro and in vivo studies in this regard have also clarified the molecular mechanisms of these effects, some of which include the improvement in glucose and lipid profiles; reduced activity of scavenger receptors, inflammatory cytokines, and oxidative stress; improvement in endothelial function; and prevention of platelet aggregation (Daleprane & Abdalla, 2013). Moreover, numerous findings have indicated that polyphenols reduce CVD risk and inhibit the formation of atherosclerosis plaques (Gorinstein et al., 2011; Grassi et al., 2008; Norata et al., 2007). Therefore, propolis is considered as an abundant source of polyphenols with a potential role in preventing cardiovascular events.

Propolis has beneficial effects on the regulation of lipid and lipoprotein metabolism. Previous findings have indicated that propolis administration led to reducing liver cholesterol and triglyceride levels and hepatic triglyceride synthesis in rats (Daleprane et al., 2012; Hu et al., 2005). Moreover, treatment with Brazilian propolis in low-density lipoprotein (LDL) receptor knockout mice decreased the levels of triacylglycerol (TAG), total cholesterol (TC), and non-HDL-C (Daleprane et al., 2012). The mice receiving propolis treatment also experienced a significant reduction in TAG and TC, as well as increased HDL-C, compared to the untreated mice. On the same note, Turkish propolis has been reported to prevent alcohol-induced acute liver injury and lipid deposition, exerting positive effects on the lipid profile. Notably, in the mice receiving propolis treatment and alcohol, HDL levels have been reported to be high, and LDL was observed to be lower compared to the mice receiving alcohol only (Kolankaya et al., 2002).

In other studies, propolis has shown favorable effects on the HDL and LDL levels of rats (Hu et al., 2005). For instance, administration of propolis in diabetic rats led to decreased levels of TC, LDL-C, very-low-density lipoprotein (VLDL), and TAG. These findings highlight the role of propolis in the regulation of lipid metabolism, as well as its contribution to the status of lipid abnormalities (Hu et al., 2005). Daleprane et al. hypothesized that propolis might prevent atherosclerosis. On the contrary, treatment of LDL receptor gene (LDLr$^{-/-}$) mice with the extracted polyphenols of propolis has been reported to decrease the area of atherosclerotic lesions (Daleprane et al., 2012) and prevent the development of atherosclerosis in the treated LDL r$^{-/-}$ mice by improving the lipid profile and downregulating pro-inflammatory cytokines, chemokines, and angiogenic factors. In the mentioned study, propolis administration also decreased the mRNA expression of several genes (MCP-1, INF-g, IL-6, CD36, and TGF-β), which play a key role in the atherosclerotic process (Daleprane et al., 2012).

Previous studies have demonstrated the beneficial effects of propolis on the lipid profile (Burdock, 1998; Castaldo & Capasso, 2002; Hu et al., 2005; Munstedt & Zymunt, 2001; Murata et al., 2004; Nader et al., 2010). For instance, Kolankaya et al. conducted an animal study and reported that the EEP at 200 mg/kg BW/day decreased LDL levels and increased HDL levels in rats (Kolankaya et al., 2002). Consistently, the results of another study indicated that the extracted polyphenols of red propolis significantly lowered TAG and TC and increased HDL-C in the LDL r$^{-/-}$ knockout mice (Daleprane et al., 2012). In a clinical trial conducted by Mujica et al., propolis supplementation for 90 days significantly increased HDL levels and decreased the systolic and diastolic blood pressure, thereby reducing the risk of CVDs (Mujica et al., 2017). In contrast, Samadi et al. indicated that supplementation with propolis (900 mg/day), in comparison with placebo, after 12 weeks had no significant effects on lipid profile (LDL, HDL, TC, TG, and VLDL) (Samadi et al., 2017). Also, Fukuda et al., in a randomized, controlled 8-week trial, investigated the effect of Brazilian green propolis (226.8 mg/day). There were no significant effects of the propolis supplements on LDL, HDL, TC, and TG (Fukuda et al., 2015). Recently, Salehi-Sahlabadi et al. (2020) in a systematic review and meta-analysis of randomized-controlled trials, indicated that propolis consumption is associated with a decrease in TG levels as well as an increase in HDL levels.

The proposed hypocholesterolemic mechanism of propolis is through the protein expression of the ATP-binding cassette (ABC) transporters A1 and G1 (ABCA1 and ABCG1) (Gorinstein et al., 2011). Various types of propolis could increase *ABCA1* gene expression (Ichi et al., 2009; Koya-Miyata et al., 2009), which in turn increases HDL and enhances the cholesterol efflux from the peripheral tissue (Chung et al., 2010; Daleprane et al., 2012; Nader et al., 2010). Therefore, propolis may improve the lipid profile by upregulating ABCA1 gene expression. In addition, the ethanol extract of Brazilian red propolis has been reported to increase the ABCA1 promoter activity in THP-1 macrophages (Iio et al., 2012). Given that patients with RA have impaired ATP-binding cassette G1-mediated CEC due to the disease activity and its complications (Ronda et al., 2014), propolis supplementation may effectively decrease the disease symptoms, thereby decreasing the risk of CVDs. Simultaneously with the increase in the ABCA1 cassette, Brazilian red propolis could upregulate ApoA-1, which is involved in the cholesterol efflux by macrophages. The effects of propolis on ABCA1 could be attributed to the activation of PPARγ and LXRα (Iio et al., 2012). Table 4 presents a summary of the animal studies regarding the effects of propolis on the lipid profile.

In vitro and in vivo data have proposed that the positive properties of propolis, which have an effect on the lipid profile, could be involved in the atheroprotective effects of this compound. Furthermore, scientific reports suggest that the polyphenols extracted from propolis may be effective in the prevention of atherosclerosis (Salehi-Sahlabadi et al., 2020; Silva et al., 2011).

Nitric oxide is an endothelium-derived relaxing factor with vasodilatory and antiaggregative properties, which protects the blood vessels at low concentrations. However, the excessive NO produced by inflammatory cells may react with other nitrogen and oxygen species and stimulate oxidative stress (Ali et al., 2014). Several studies have reported increased NO levels in the serum of patients with RA (Ali et al., 2014; Ersoy et al., 2002; Mahmoud & Ismail, 2011). According to an animal study, propolis intake in diabetic mice resulted in the reduction of NO and NOS levels (Hu et al., 2005). Propolis reduces NO levels by decreasing NOS activity, thereby protecting the

TABLE 4 Summary of animal studies on effects of propolis on lipid profile

First author (year)	Country	Animal species	Propolis dosage	Duration (day)	Outcomes	Reference
Kolankaya et al. (2002)	Turkey	Rat	200 mg/kg/day	15	↓ TC and TG ↑HDL-C	Kolankaya et al. (2002)
Hu et al. (2005)	China	Rat	1 ml/100 g	56	↓ TC, TG, LDL-C, and VLDL-C ↑ HDL-C	Hu et al. (2005)
Abo-Salem et al. (2009)	Egypt	Rat	100, 200, and 300 mg/kg/day	40	↓ Cholesterol, TG, LDL-C, and VLDL-C ↑ HDL-C	Abo-Salem et al. (2009)
Nader et al. (2010)	Egypt	Rabbit	75 mg/kg/day	28	↓ TC, TG, and LDL-C ↑ HDL-C	Nader et al. (2010)
Zhu et al. (2011)	China	Rat	10-mg propolis per 100 g/kg/day	56	↓ TC	Zhu, Li, et al. (2011)
Bhadauria (2011)	India	Rat	200 mg/kg	14	↓ TG and TC	Bhadauria (2012)
Li et al. (2012)	China	Rat	50, 100, and 200 mg/kg/day	70	↓ TG ↔ TC, HDL-C, and LDL-C	Li et al. (2012)
Fang et al. (2013)	China	Mice	160 mg/kg/day	98	↓ TC, TG, and non-HDL-C	Fang et al. (2013)
Newairy et al. (2013)	Egypt	Rat	50 mg/kg/day	28	Normalized the TC, TG, and LDL-C ↑ HDL-C	Newairy and Abdou (2013)
Alqayim (2015)	Iraq	Rabbit	50 mg/kg/day	60	↓ TC, TAG, and LDL-C ↑ HDL-C	Alqayim (2015)
Al Ghamdi et al. (2015)	Saudi Arabia	Mice	100 mg/kg/day	28	↓ LDL-C ↑ HDL-C	Al Ghamdi et al. (2015)
Elissa et al. (2015)	Egypt	Rat	0.6 g/kg/day	21	↓ TC, LDL-C, and TG ↑ HDL-C	Elissa et al. (2015)
Albokhadaim (2015)	Saudi Arabia	Rat	1% and 2% of cholesterol diet	14	↓ TG and TC	Albokhadaim (2015)
Kismet et al. (2017)	Turkey	Rat	200 mg/kg/day	14	↓ TC, non-HDL-C, and TG	Kemal Kismet et al. (2017)
Gong et al. (2017)	China	Mice	10 μmol/kg/day	28	↓ TC, TG, and LDL-C ↑ HDL-C	Gong et al. (2017)
Chen et al. (2018)	Taiwan	Rat	183.9 and 919.5 mg/kg/day	56	↓ TC, LDL-C, and TG ↑ HDL-C	Chen et al. (2018)
Ibrahima et al. (2019)	Egypt	Rat	100 mg/kg/day	28	↓ TC, LDL-C, and TG ↑ HDL-C	Ibrahim et al. (2019)

Abbreviations: ↑, increase; ↓, decrease; ↔, no effect; C, control; HDL, high-density lipoprotein; LDL, low-density lipoprotein; T, treatment; TC, total cholesterol; TG, triglyceride.

endothelial cells of the blood vessels. Furthermore, the EEP could prevent NO production by reducing iNOS expression in Raw 264.7 macrophages and inhibiting the catalytic activity of iNOS. On the contrary, excessive NO production is involved in the cardiovascular inflammatory process, and propolis may affect the regulation of NO levels through its anti-inflammatory activities.

2.5 | Strengths and limitations

This review study aimed to assess the effects of propolis on inflammation, oxidative stress, and cardiometabolic indices in RA patients. The main limitation of our study was the heterogeneity of the reported data in the reviewed studies, and quality assessment of the studies might have led to more accurate results for the generalization of the data. To the best of our knowledge, this is the first review study that has gathered an in-depth scientific demonstration of the possible effects of propolis on patients with RA.

3 | CONCLUSION

The present study suggested that propolis may have beneficial effects on oxidative stress biomarkers and inflammation process in RA patients due to its potent antioxidant and polyphenolic properties. Further studies particularly clinical trials must be conducted to demonstrate the definitive effects of propolis on multiple aspects of RA disease.

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CONFLICTS OF INTEREST

The authors also declare that they have no conflict of interest.

ETHICAL APPROVAL

No ethical approval was required, as this is a review article with no original research data.

INFORMED CONSENT

There were no study participants in this review article, and informed consent was not required.

DATA AVAILABILITY STATEMENT

All the data used in this study can be made available on reasonable request.

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REFERENCES

Abass, A. O., Kamel, N. N., Khalifa, W. H., Gouda, G., El-Manylawi, M., Mehaisen, G. M., & Mashaly, M. M. (2017). Propolis supplementation attenuates the negative effects of oxidative stress induced by paraquat injection on productive performance and immune function in turkey poults. *Poultry Science*, *96*(12), 4419–4429. https://doi.org/10.3382/ps/pex248

Abdel-Rahman, R. F., Alqasoumi, S. I., Ogaly, H. A., Abd-Elsalam, R. M., El-Banna, H. A., & Soliman, G. A. (2020). Propolis ameliorates cerebral injury in focal cerebral ischemia/reperfusion (I/R) rat model via upregulation of TGF-β1. *Saudi Pharmaceutical Journal*, *28*(1), 116–126. https://doi.org/10.1016/j.jsps.2019.11.013

Abo-Salem, O. M., El-Edel, R. H., Harisa, G. E., El-Halawany, N., & Ghonaim, M. M. (2009). Experimental diabetic nephropathy can be prevented by propolis: effect on metabolic disturbances and renal oxidative parameters. *Pakistan Journal of Pharmaceutical Sciences*, *22*(2), 205–210.

Abou-Zeid, A., El-Damarawy, S., Mariey, Y., & El-Kasass, S. (2015). Effect of dietary propolis supplementation on performance and activity of antioxidant enzymes in broiler chickens. *Egyptian Journal of Nutrition and Feeds*, *18*(2 Special), 391–400. https://doi.org/10.21608/ejnf.2015.104498

Afsharpour, F., Hashemipour, S., Khadem-Haghighian, H., & Koushan, Y. J. J. (2017). Effects of Iranian propolis on glycemic status, inflammatory factors, and liver enzyme levels in type 2 diabetic patients: A randomized, double-blind, placebo-controlled, clinical trial. *Scientific Reports*, *9*, 9–14.

Afsharpour, F., Javadi, M., Hashemipour, S., Koushan, Y., & haghighian, H. K. (2019). Propolis supplementation improves glycemic and antioxidant status in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study. *Complementary Therapies in Medicine*, *43*, 283–288. https://doi.org/10.1016/j.ctim.2019.03.001

Ahmed, R., Tanvir, E., Hossen, M., Afroz, R., Ahmmed, I., Rumpa, N.-E., Paul, S., Gan, S. H., Sulaiman, S. A., & Khalil, M. I. (2017). Antioxidant properties and cardioprotective mechanism of malaysian propolis in rats. *Evidence-Based Complementary and Alternative Medicine*, *2017*, 1–11. https://doi.org/10.1155/2017/5370545

Akyol, Ö., İşçi, N., Temel, İ., Özgöçmen, S., Uz, E., Murat, M., & Büyükberber, S. (2001). The relationships between plasma and erythrocyte antioxidant enzymes and lipid peroxidation in patients with rheumatoid arthritis. *Joint Bone Spine*, *68*(4), 311–317. https://doi.org/10.1016/S1297-319X(01)00279-2

Al Ghamdi, A. A., Badr, G., Hozzein, W. N., Allam, A., Al-Waili, N. S., Al-Wadaan, M. A., & Garraud, O. (2015). Oral supplementation of diabetic mice with propolis restores the proliferation capacity and chemotaxis of B and T lymphocytes towards CCL21 and CXCL12 by modulating the lipid profile, the pro-inflammatory cytokine levels and oxidative stress. *BMC Immunology*, *16*(1), 54. https://doi.org/10.1186/s12865-015-0117-9

Albokhadaim, I. (2015). Influence of dietary supplementation of propolis on hematology, biochemistry and lipid profile of rats fed high cholesterol diet. *Journal of Advanced Veterinary and Animal Research*, *2*(1), 56–63. https://doi.org/10.5455/javar.2015.b49

Al-Hariri, M. T., Eldin, T. A. G., & Al-Harb, M. M. (2016). Protective effect and potential mechanisms of propolis on streptozotocin-induced diabetic rats. *Journal of Taibah University Medical Sciences*, *11*(1), 7–12. https://doi.org/10.1016/j.jtumed.2015.11.002

Ali, A. M., Habeeb, R. A., El-Azizi, N. O., Khattab, D. A., Abo-Shady, R. A., & Elkabarity, R. H. (2014). Higher nitric oxide levels are associated with disease activity in Egyptian rheumatoid arthritis patients. *Revista Brasileira de Reumatologia (English Edition)*, *54*(6), 446–451. https://doi.org/10.1016/j.rbre.2014.07.002

Alm-Eldeen, A., Basyony, M., Elfiky, N., & Ghalwash, M. (2017). Effect of the Egyptian propolis on the hepatic antioxidant defense and pro-apoptotic p53 and anti-apoptotic bcl2 expressions in aflatoxin B1 treated male mice. *Biomedicine & Pharmacotherapy*, *87*, 247–255. https://doi.org/10.1016/j.biopha.2016.12.084

Alqayim, M. A. J. (2015). Propolis cardio protective role from the impact of aluminum chloride in female rabbits. *Basrah Journal of Veterinary Research*, *14*, 136–149.

Alyane, M., Kebsa, L. B. W., Boussenane, H., Rouibah, H., & Lahouel, M. (2008). Cardioprotective effects and mechanism of action of polyphenols extracted from propolis against doxorubicin toxicity. *Pakistan Journal of Pharmaceutical Sciences*, *21*(3), 201–209.

Ansorge, S., Reinhold, D., & Lendeckel, U. (2003). Propolis and some of its constituents down-regulate DNA synthesis and inflammatory cytokine production but induce TGF-β1 production of human immune cells. *Zeitschrift für Naturforschung C*, *58*(7–8), 580–589. https://doi.org/10.1515/znc-2003-7-823

Araujo, M. A., Libério, S. A., Guerra, R. N., Ribeiro, M. N. S., & Nascimento, F. R. F. (2012). Mechanisms of action underlying the anti-inflammatory and immunomodulatory effects of propolis: A brief review. *Revista Brasileira De Farmacognosia*, *22*(1), 208–219

Attia, A. A., Elmazoudy, R. H., & El-Shenawy, N. S. (2012). Antioxidant role of propolis extract against oxidative damage of testicular tissue induced by insecticide chlorpyrifos in rats. *Pesticide Biochemistry and Physiology*, *103*(2), 87–93. https://doi.org/10.1016/j.pestbp.2012.04.002

Aviña-Zubieta, J. A., Choi, H. K., Sadatsafavi, M., Etminan, M., Esdaile, J. M., & Lacaille, D. (2008). Risk of cardiovascular mortality in patients with rheumatoid arthritis: A meta-analysis of observational studies. *Arthritis Care & Research*, *59*(12), 1690–1697. https://doi.org/10.1002/art.24092

Aydın, E., Hepokur, C., Mısır, S., & Yeler, H. (2018). Effects of propolis on oxidative stress in rabbits undergoing implant. *Surgery*, *21*(2), 136–144. https://doi.org/10.7126/cumudj.356554

Bae, S. C., Kim, S. J., & Sung, M. K. (2003). Inadequate antioxidant nutrient intake and altered plasma antioxidant status of rheumatoid arthritis patients. *Journal of the American College of Nutrition*, *22*(4), 311–315. https://doi.org/10.1080/07315724.2003.10719309

Baeuerle, P. A. (1991). The inducible transcription activator NF-κB: Regulation by distinct protein subunits. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, *1072*(1), 63–80. https://doi.org/10.1016/0304-419X(91)90007-8

Balkarli, A., & Cobankara, V. (2016). Pulmonary nodulosis associated with leflunomide therapy in rheumatoid arthritis: Report of four cases and review of the literature. *Journal of Clinical and Experimental Investigations*, *7*(1), 98–102.

Bankova, V. (2005). Chemical diversity of propolis and the problem of standardization. *Journal of Ethnopharmacology*, *100*(1–2), 114–117. https://doi.org/10.1016/j.jep.2005.05.004

Banskota, A. H., Tezuka, Y., & Kadota, S. (2001). Recent progress in pharmacological research of propolis. *Phytotherapy Research*, *15*(7), 561–571. https://doi.org/10.1002/ptr.1029

Barlak, Y., Değer, O., Çolak, M., Karataylı, S. C., Bozdayı, A. M., & Yücesan, F. (2011). Effect of Turkish propolis extracts on proteome of prostate cancer cell line. *Proteome Science*, *9*(1), 1–11. https://doi.org/10.1186/1477-5956-9-74

Bauerova, K., & Bezek, S. (2000). Role of reactive oxygen and nitrogen species in etiopathogenesis of rheumatoid arthritis. *General Physiology and Biophysics*, *18*, 15–20.

Baykalir, B. G., Seven, P. T., Gur, S., & Seven, I. J. A. R. (2018). The effects of propolis on sperm quality, reproductive organs and testicular antioxidant status of male rats treated with cyclosporine-A. *Animal Reproduction*, *13*(2), 105–111.

Bazmandegan, G., Boroushaki, M. T., Shamsizadeh, A., Ayoobi, F., Hakimizadeh, E., & Allahtavakoli, M. (2017). Brown propolis attenuates cerebral ischemia-induced oxidative damage via affecting antioxidant enzyme system in mice. *Biomedicine & Pharmacotherapy*, *85*, 503–510. https://doi.org/10.1016/j.biopha.2016.11.057

Bhadauria, M. (2012). Propolis prevents hepatorenal injury induced by chronic exposure to carbon tetrachloride. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 1–12. https://doi.org/10.1155/2012/235358

Boers, M., Nurmohamed, M., Doelman, C., Lard, L., Verhoeven, A., Voskuyl, A., & van der Linden, S. (2003). Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *62*(9), 842–845. https://doi.org/10.1136/ard.62.9.842

Bors, W., Heller, W., Michel, C., & Saran, M. (1990). [36] Flavonoids as antioxidants: Determination of radical-scavenging efficiencies. *Methods in Enzymology*, *186*, 343–355.

Boufadi, M. Y., Soubhye, J., & Van Antwerpen, P. (2021). Anti-inflammatory, antioxidant effects, and bioaccessibility of Tigzirt propolis. *Journal of Food Biochemistry*, *45*, e13663. https://doi.org/10.1111/jfbc.13663

Bueno-Silva, B., Rosalen, P. L., Alencar, S. M., & Mayer, M. P. (2017). Anti-inflammatory mechanisms of neovestitol from Brazilian red propolis in LPS-activated macrophages. *Journal of Functional Foods*, *36*, 440–447. https://doi.org/10.1016/j.jff.2017.07.029

Burdock, G. (1998). Review of the biological properties and toxicity of bee propolis (propolis). *Food and Chemical Toxicology*, *36*(4), 347–363. https://doi.org/10.1016/S0278-6915(97)00145-2

Cardoso, S. M., Ribeiro, M., Ferreira, I. L., & Rego, A. C. (2011). Northeast Portuguese propolis protects against staurosporine and hydrogen peroxide-induced neurotoxicity in primary cortical neurons. *Food and Chemical Toxicology*, *49*(11), 2862–2868. https://doi.org/10.1016/j.fct.2011.08.010

Castaldo, S., & Capasso, F. (2002). Propolis, an old remedy used in modern medicine. *Fitoterapia*, *73*, S1–S6. https://doi.org/10.1016/S0367-326X(02)00185-5

Charles-Schoeman, C., Lee, Y. Y., Grijalva, V., Amjadi, S., FitzGerald, J., Ranganath, V. K., Taylor, M., McMahon, M., Paulus, H. E., & Reddy, S. T. (2012). Cholesterol efflux by high density lipoproteins is impaired in patients with active rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *71*(7), 1157–1162. https://doi.org/10.1136/annrheumdis-2011-200493

Charles-Schoeman, C., Watanabe, J., Lee, Y. Y., Furst, D. E., Amjadi, S., Elashoff, D., Park, G., McMahon, M., Paulus, H. E., Fogelman, A. M., & Reddy, S. T. (2009). Abnormal function of high-density lipoprotein is associated with poor disease control and an altered protein cargo in rheumatoid arthritis. *Arthritis & Rheumatism*, *60*(10), 2870–2879. https://doi.org/10.1002/art.24802

Chen, L.-H., Chien, Y.-W., Chang, M.-L., Hou, C.-C., Chan, C.-H., Tang, H.-W., & Huang, H.-Y.-J.-N. (2018). Taiwanese green propolis ethanol extract delays the progression of type 2 diabetes mellitus in rats treated with streptozotocin/high-fat diet. *Nutrients*, *10*(4), 503. https://doi.org/10.3390/nu10040503

Cheung, K.-W., Sze, D.-M.-Y., Chan, W. K., Deng, R.-X., Tu, W., & Chan, G. C.-F. (2011). Brazilian green propolis and its constituent, artepillin C inhibits allogeneic activated human CD4 T cells expansion and activation. *Journal of Ethnopharmacology*, *138*(2), 463–471.

Chopra, S., Pillai, K., Husain, S., & Girl, D. K. (1995). Propolis protects against doxorubicin-induced myocardiopathy in rats. *Experimental and Molecular Pathology*, *62*(3), 190–198. https://doi.org/10.1006/exmp.1995.1021

Chung, S., Timmins, J. M., Duong, M. N., Degirolamo, C., Rong, S., Sawyer, J. K., Singaraja, R. R., Hayden, M. R., Maeda, N., Rudel, L. L., Shelness, G. S., & Parks, J. S. (2010). Targeted deletion of hepatocyte ABCA1 leads to very low density lipoprotein triglyceride overproduction and low density lipoprotein hypercatabolism. *Journal of Biological Chemistry*, *285*(16), 12197–12209. https://doi.org/10.1074/jbc.M109.096933

Corrêa, F. R. S., Schanuel, F. S., Moura-Nunes, N., Monte-Alto-Costa, A., & Daleprane, J. B. (2017). Brazilian red propolis improves cutaneous wound healing suppressing inflammation-associated transcription factor NFκB. *Biomedicine & Pharmacotherapy*, *86*, 162–171. https://doi.org/10.1016/j.biopha.2016.12.018

Daleprane, J. B., & Abdalla, D. S. Emerging roles of propolis: Antioxidant, cardioprotective, and antiangiogenic actions. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–8. https://doi.org/10.1155/2013/175135

Daleprane, J. B., da Silva Freitas, V., Pacheco, A., Rudnicki, M., Faine, L. A., Dörr, F. A., Ikegaki, M., Salazar, L. A., Ong, T. P., & Abdalla, D. S. P. (2012). Anti-atherogenic and anti-angiogenic activities of polyphenols from propolis. *The Journal of Nutritional Biochemistry*, *23*(6), 557–566. https://doi.org/10.1016/j.jnutbio.2011.02.012

Darvishi, N., Yousefinejad, V., Akbari, M. E., Abdi, M., Moradi, N., Darvishi, S., Mehrabi, Y., Ghaderi, E., Jamshidi-Naaeini, Y., Ghaderi, B., & Davoodi, S. H. (2020). Antioxidant and anti-inflammatory effects of oral propolis in patients with breast cancer treated with chemotherapy: A Randomized controlled trial. *Journal of Herbal Medicine*, *23*, 100385. https://doi.org/10.1016/j.hermed.2020.100385

Das, D. C., Jahan, I., Uddin, M. G., Hossain, M. M., Chowdhury, M. A. Z., Fardous, Z., Rahman, M. M., Kabir, A. K. M. H., Deb, S. R., Siddique, M. A. B., & Das, A. (2020). Serum CRP, MDA, vitamin C, and trace elements in Bangladeshi patients with rheumatoid arthritis. *Biological Trace Element Research*, *199*(1), 76–84. https://doi.org/10.1007/s12011-020-02142-7

De Almeida, E., & Menezes, H. (2002). Anti-inflammatory activity of propolis extracts: A review. *Journal of Venomous Animals and Toxins*, *8*(2), 191–212. https://doi.org/10.1590/S0104-79302002000200002

Ebeid, S. A., Abd El Moneim, N. A., El-Benhawy, S. A., Hussain, N. G., & Hussain, M. I. (2016). Assessment of the radioprotective effect of propolis in breast cancer patients undergoing radiotherapy. New perspective for an old honey bee product. *Journal of Radiation Research and Applied Sciences*, *9*(4), 431–440.

El Rabey, H. A., Al-Seeni, M. N., & Bakhashwain, A. S. (2017). The antidiabetic activity of *Nigella sativa* and propolis on streptozotocin-induced diabetes and diabetic nephropathy in male rats. *Evidence-Based Complementary and Alternative Medicine*, *2017*, 5439645. https://doi.org/10.1155/2017/5439645

El-Awady, M. S., El-Agamy, D. S., Suddek, G. M., & Nader, M. A. (2014). Propolis protects against high glucose-induced vascular endothelial dysfunction in isolated rat aorta. *Journal of Physiology and Biochemistry*, *70*(1), 247–254. https://doi.org/10.1007/s13105-013-0299-7

Elissa, L. A., Elsherbiny, N. M., & Magmomah, A. O. (2015). Propolis restored adiponectin level in type 2 diabetes through PPARγ activation. *Egyptian Journal of Basic and Applied Sciences*, *2*(4), 318–326. https://doi.org/10.1016/j.ejbas.2015.06.003

El-Sayed, E.-S., Abo-Salem, O., Aly, H., & Mansour, A. (2009). Potential antidiabetic and hypolipidemic effects of propolis extract in streptozotocin-induced diabetic rats. *Pakistan Journal of Pharmaceutical Sciences*, *22*, 168–174.

Ernst, E. (2010). Herbal medicine in the treatment of rheumatic diseases. *Rheumatic Diseases Clinics of North America*, *37*(1), 95–102. https://doi.org/10.1016/j.rdc.2010.11.004

Ersoy, Y., Özerol, E., Baysal, Ö., Temel, I., MacWalter, R., Meral, Ü., & Altay, Z. (2002). Serum nitrate and nitrite levels in patients with rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. *Annals of the Rheumatic Diseases*, *61*(1), 76–78. https://doi.org/10.1136/ard.61.1.76

Fang, Y., Sang, H., Yuan, N., Sun, H., Yao, S., Wang, J., & Qin, S. (2013). Ethanolic extract of propolis inhibits atherosclerosis in ApoE-knockout mice. *Lipids in Health and Disease*, *12*(1), 1–6. https://doi.org/10.1186/1476-511X-12-123

Farooqui, T. (2012). Beneficial effects of propolis on human health and neurological diseases. *Frontiers in Bioscience*, *E4*(2), 779–793. https://doi.org/10.2741/e418

Filippin, L. I., Vercelino, R., Marroni, N., & Xavier, R. M. (2008). Redox signalling and the inflammatory response in rheumatoid arthritis. *Clinical & Experimental Immunology*, *152*(3), 415–422. https://doi.org/10.1111/j.1365-2249.2008.03634.x

Fox, D. A. (2005). *Etiology and pathogenesis of rheumatoid arthritis*.

Fuat Gulhan, M., Duran, A., Selamoglu Talas, Z., Kakoolaki, S., & Mansouri, S. M. (2012). Effects of propolis on microbiologic and biochemical parameters of rainbow trout (*Oncorhynchus mykiss*) after exposure to the pesticide. *Iranian Journal of Fisheries Sciences*, *11*(3), 490–503.

Fukuda, T., Fukui, M., Tanaka, M., Senmaru, T., Iwase, H., Yamazaki, M., Aoi, W., Inui, T., Nakamura, N., & Marunaka, Y. (2015). Effect of Brazilian green propolis in patients with type 2 diabetes: A double-blind randomized placebo-controlled study. *Biomedical Reports*, *3*(3), 355–360. https://doi.org/10.3892/br.2015.436

Furst, D. E., Schiff, M. H., Fleischmann, R. M., Strand, V., Birbara, C. A., Compagnone, D., … Chartash, E. K. (2003). Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: Results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *Journal of Rheumatology*, *30*(12), 2563–2571.

Gao, W., Pu, L., Wei, J., Yao, Z., Wang, Y., Shi, T., Zhao, L., Jiao, C., & Guo, C. (2018). Serum antioxidant parameters are significantly increased in patients with type 2 diabetes mellitus after consumption of Chinese propolis: A randomized controlled trial based on fasting serum glucose level. *Diabetes Therapy*, *9*(1), 101–111. https://doi.org/10.1007/s13300-017-0341-9

Garoui, E. M., Troudi, A., Fetoui, H., Soudani, N., Boudawara, T., & Zeghal, N. (2012). Propolis attenuates cobalt induced-nephrotoxicity in adult rats and their progeny. *Experimental and Toxicologic Pathology*, *64*(7-8), 837–846. https://doi.org/10.1016/j.etp.2011.03.004

Gautam, R., & Jachak, S. M. (2009). Recent developments in anti-inflammatory natural products. *Medicinal Research Reviews*, *29*(5), 767–820. https://doi.org/10.1002/med.20156

Georgetti, S. R., Casagrande, R., Di Mambro, V. M., Azzolini, A. E., & Fonseca, M. J. (2003). Evaluation of the antioxidant activity of different flavonoids by the chemiluminescence method. *American Association of Pharmaceutical Scientists*, *5*(2), 111–115. https://doi.org/10.1208/ps050220

Gholaminejad, F., Javadi, M., Karami, A. A., Alizadeh, F., Kavianpour, M., & Khadem Haghighian, H. (2019). Propolis supplementation effects on semen parameters, oxidative stress, inflammatory biomarkers and reproductive hormones in infertile men with asthenozoospermia. A randomized clinical trial. *International Journal of Medical Laboratory*, *6*(1), 21–32. https://doi.org/10.18502/ijml.v6i1.504

Gokhan, E. (2007). Evaluation of propolis effects on some biochemical parameters in rats treated with sodium xuoride. *Pesticide Biochemistry and Physiology*, *88*, 273–283.

Gong, P., Chang, X., Chen, X., Bai, X., Wen, H., Pi, S., Chen, F. (2017). Metabolomics study of cadmium-induced diabetic nephropathy and protective effect of caffeic acid phenethyl ester using UPLC–Q-TOF-MS combined with pattern recognition. *Environmental Toxicology and Pharmacology*, *54*, 80–92. https://doi.org/10.1016/j.etap.2017.06.021

González-Gay, M. A., & González-Juanatey, C. (2014). *Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox*. BMJ Publishing Group Ltd.

Gonzalez-Gay, M. A., Gonzalez-Juanatey, C., Lopez-Diaz, M. J., Piñeiro, A., Garcia-Porrua, C., Miranda-Filloy, J. A., Ollier, W. E. R., Martin, J., & Llorca, J. (2007). HLA–DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis & Rheumatism*, *57*(1), 125–132. https://doi.org/10.1002/art.22482

Gonzalez-Gay, M. A., Gonzalez-Juanatey, C., & Martin, J. (2005). Rheumatoid arthritis: A disease associated with accelerated atherogenesis. *Seminars in Arthritis and Rheumatism*, *35*(1), 8–17. https://doi.org/10.1016/j.semarthrit.2005.03.004

Gorinstein, S., Leontowicz, H., Leontowicz, M., Jesion, I., Namiesnik, J., Drzewiecki, J., Park, Y.-S., Ham, K.-S., Giordani, E., & Trakhtenberg, S. (2011). Influence of two cultivars of persimmon on atherosclerosis indices in rats fed cholesterol-containing diets: Investigation in vitro and in vivo. *Nutrition*, *27*(7–8), 838–846. https://doi.org/10.1016/j.nut.2010.08.015

Grassi, D., Aggio, A., Onori, L., Croce, G., Tiberti, S., Ferri, C., Ferri, L., & Desideri, G. (2008). Tea, flavonoids, and nitric oxide-mediated vascular reactivity. *The Journal of Nutrition*, *138*(8), 1554S–1560S. https://doi.org/10.1093/jn/138.8.1554S

Halliwell, B., Hoult, J. R., & Blake, D. R. (1988). Oxidants, inflammation, and anti-inflammatory drugs. *The FASEB Journal*, *2*(13), 2867–2873. https://doi.org/10.1096/fasebj.2.13.2844616

Helli, B., Mowla, K., Mohammadshahi, M., & Jalali, M. (2016). Effect of sesamin supplementation on cardiovascular risk factors in women with rheumatoid arthritis. *Journal of the American College of Nutrition*, *35*(4), 300–307. https://doi.org/10.1080/07315724.2015.1005198

Hemieda, F. A., El-Kholy, W. M., Wafaa, E., El-Sawah, M., & Shady, G. J. (2015). Influence of propolis on oxidative stress, inflammation and apoptosis in streptozotocin induced diabetic rats. *International Journal of Advanced Research*, *3*(7), 831–845.

Hesami, S., Hashemipour, S., Shiri-Shahsavar, M. R., Koushan, Y., & Haghighian, H. K. (2019). Administration of Iranian Propolis attenuates oxidative stress and blood glucose in type II diabetic patients: A randomized, double-blind, placebo-controlled, clinical trial. *Caspian Journal of Internal Medicine*, *10*(1), 48.

Hu, F., Hepburn, H., Li, Y., Chen, M., Radloff, S., & Daya, S. (2005). Effects of ethanol and water extracts of propolis (bee glue) on acute inflammatory animal models. *Journal of Ethnopharmacology*, *100*(3), 276–283. https://doi.org/10.1016/j.jep.2005.02.044

Ibrahim, K. A., Khwanes, S. A., El-Desouky, M. A., & Elhakim, H. K. A. (2019). Propolis relieves the cardiotoxicity of chlorpyrifos in diabetic rats via alleviations of paraoxonase-1 and xanthine oxidase genes expression. *Pesticide Biochemistry and Physiology*, *159*, 127–135. https://doi.org/10.1016/j.pestbp.2019.06.006

Ichi, I., Hori, H., Takashima, Y., Adachi, N., Kataoka, R., Okihara, K., Hashimoto, K., & Kojo, S. (2009). The beneficial effect of propolis on fat accumulation and lipid metabolism in rats fed a high-fat diet. *Journal of Food Science*, *74*(5), H127–H131. https://doi.org/10.1111/j.1750-3841.2009.01147.x

Ichikawa, H., Satoh, K., Tobe, T., Yasuda, I., Ushio, F., Matsumoto, K., Endo, K., & Ookubo, C. (2002). Free radical scavenging activity of propolis. *Redox Report*, *7*(5), 347–350. https://doi.org/10.1179/135100002125000965

Iio, A., Ohguchi, K., Maruyama, H., Tazawa, S., Araki, Y., Ichihara, K., Nozawa, Y., & Ito, M. (2012). Ethanolic extracts of Brazilian red propolis increase ABCA1 expression and promote cholesterol efflux from THP-1 macrophages. *Phytomedicine*, *19*(5), 383–388. https://doi.org/10.1016/j.phymed.2011.10.007

Ilhan, A., Koltuksuz, U., Ozen, S., Uz, E., Ciralik, H., & Akyol, O. (1999). The effects of caffeic acid phenethyl ester (CAPE) on spinal cord ischemia/reperfusion injury in rabbits. *European Journal of Cardio-Thoracic Surgery*, *16*(4), 458–463. https://doi.org/10.1016/s1010-7940(99)00246-8

Iwakura, Y., & Ishigame, H. (2006). The IL-23/IL-17 axis in inflammation. *Journal of Clinical Investigation*, *116*(5), 1218–1222. https://doi.org/10.1172/JCI28508

Jalali, M., Ranjbar, T., Mosallanezhad, Z., Mahmoodi, M., Moosavian, S. P., Ferns, G., … Sohrabi, Z. J. (2020). Effect of propolis supplementation on serum CRP and TNF-α levels in adults: A systematic review and meta-analysis of clinical trials. *Complementary Therapies in Medicine*, *50*, 102380.

Jasprica, I., Mornar, A., Debeljak, Ž., Smolčić-Bubalo, A., Medić-Šarić, M., Mayer, L., Romić, Ž., Bućan, K., Balog, T., Sobočanec, S., & Šverko, V. (2007). In vivo study of propolis supplementation effects on antioxidative status and red blood cells. *Journal of Ethnopharmacology*, *110*(3), 548–554. https://doi.org/10.1016/j.jep.2006.10.023

Kalpakcioglu, B., & Şenel, K. (2008). The interrelation of glutathione reductase, catalase, glutathione peroxidase, superoxide dismutase, and glucose-6-phosphate in the pathogenesis of rheumatoid arthritis. *Clinical Rheumatology*, *27*(2), 141–145. https://doi.org/10.1007/s10067-007-0746-3

Kamanlı, A., Nazıroğlu, M., Aydılek, N., & Hacıevlıyagil, C. (2004). Plasma lipid peroxidation and antioxidant levels in patients with rheumatoid arthritis. *Cell Biochemistry and Function*, *22*(1), 53–57. https://doi.org/10.1002/cbf.1055

Kanbur, M., Eraslan, G., Silici, S. J. E., & Safety, E. (2009). Antioxidant effect of propolis against exposure to propetamphos in rats. *Ecotoxicology and Environmental Safety*, *72*(3), 909–915. https://doi.org/10.1016/j.ecoenv.2007.12.018

Kao, T.-K., Ou, Y.-C., Raung, S.-L., Lai, C.-Y., Liao, S.-L., & Chen, C.-J. (2010). Inhibition of nitric oxide production by quercetin in endotoxin/cytokine-stimulated microglia. *Life Sciences*, *86*(9-10), 315–321. https://doi.org/10.1016/j.lfs.2009.12.014

Kaur, A., Nain, P., & Nain, J. (2012). Herbal plants used in treatment of rheumatoid arthritis: A review. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(Suppl 4), 44–57.

Khalil, F. A., & El-Sheikh, N. (2010). The effects of dietary Egyptian propolis and bee pollen supplementation against toxicity if sodium fluoride in rats. *Journal of American Science*, *11*(6), 310–316.

Khayyal, M. T., el-Ghazaly, M. A., El-Khatib, A. S., Hatem, A. M., de Vries, P. J., el-Shafei, S., & Khattab, M. M. (2003). A clinical pharmacological study of the potential beneficial effects of a propolis food product as an adjuvant in asthmatic patients. *Fundamental & Clinical Pharmacology*, *17*, 93–102.

Kismet, K., Ozcan, C., Kuru, S., Gencay Celemli, O., Celepli, P., Senes, M., Guclu, T., Sorkun, K., Hucumenoglu, S., & Besler, T. (2017). Does propolis have any effect on non-alcoholic fatty liver disease? *Biomedicine & Pharmacotherapy*, *90*, 863–871. https://doi.org/10.1016/j.biopha.2017.04.062

Kismet, K., Sabuncuoglu, M. Z., Kilicoglu, S. S., Kilicoglu, B., Devrim, E., Erel, S., Sunay, A. E., Erdemli, E., Durak, I., & Akkus, M. A. (2008). Effect of propolis on oxidative stress and histomorphology of liver tissue in experimental obstructive jaundice. *European Surgical Research*, *41*(2), 231–237. https://doi.org/10.1159/000136479

Kiziltunc, A., Coğalgil, S., & Cerrahoğlu, L. (1998). Carnitine and antioxidants levels in patients with rheumatoid arthritis. *Scandinavian Journal of Rheumatology*, *27*(6), 441–445. https://doi.org/10.1080/030097498442271

Koenders, M. I., Lubberts, E., Oppers-Walgreen, B., van den Bersselaar, L., Helsen, M. M., Kolls, J. K., Joosten, L. A. B., & van den Berg, W. B. (2005). Induction of cartilage damage by overexpression of T cell interleukin-17A in experimental arthritis in mice deficient in interleukin-1. *Arthritis & Rheumatism*, *52*(3), 975–983. https://doi.org/10.1002/art.20885

Kolankaya, D., Selmanoğlu, G., Sorkun, K., & Salih, B. (2002). Protective effects of Turkish propolis on alcohol-induced serum lipid changes and liver injury in male rats. *Food Chemistry*, *78*(2), 213–217. https://doi.org/10.1016/S0308-8146(01)00400-9

Koya-Miyata, S., Arai, N., Mizote, A., Taniguchi, Y., Ushio, S., Iwaki, K., & Fukuda, S. (2009). Propolis prevents diet-induced hyperlipidemia and mitigates weight gain in diet-induced obesity in mice. *Biological and Pharmaceutical Bulletin*, *32*(12), 2022–2028. https://doi.org/10.1248/bpb.32.2022

Kujumgiev, A., Tsvetkova, I., Serkedjieva, Y., Bankova, V., Christov, R., & Popov, S. (1999). Antibacterial, antifungal and antiviral activity of propolis of different geographic origin. *Journal of Ethnopharmacology*, *64*(3), 235–240. https://doi.org/10.1016/S0378-8741(98)00131-7

Kurek-Górecka, A., Rzepecka-Stojko, A., Górecki, M., Stojko, J., Sosada, M., & Swierczek-Zieba, G. (2013). Structure and antioxidant activity of polyphenols derived from propolis. *Molecules (Basel, Switzerland)*, *19*(1), 78–101. https://doi.org/10.3390/molecules19010078

Laveti, D., Kumar, M., Hemalatha, R., Sistla, R., Gm Naidu, V., Talla, V., … Targets, A.-D. (2013). Anti-inflammatory treatments for chronic diseases: A review. *Inflammation & Allergy: Drug Targets*, *12*(5), 349–361.

Lee, H. N., Shin, S. A., Choo, G. S., Kim, H. J., Park, Y. S., Kim, B. S., Kim, S. K., Cho, S. D., Nam, J. S., Choi, C. S., Che, J. H., Park, B. K., & Jung, J. Y. (2018). Anti-inflammatory effect of quercetin and galangin in LPS-stimulated RAW264.7 macrophages and DNCB-induced atopic dermatitis animal models. *International Journal of Molecular Medicine*, *41*(2), 888–898. https://doi.org/10.3892/ijmm.2017.3296

Lee, Y., Shin, D.-H., Kim, J.-H., Hong, S., Choi, D., Kim, Y.-J., Kwak, M.-K., & Jung, Y. (2010). Caffeic acid phenethyl ester-mediated Nrf2 activation and IκB kinase inhibition are involved in NFκB inhibitory effect: Structural analysis for NFκB inhibition. *European Journal of Pharmacology*, *643*(1), 21–28. https://doi.org/10.1016/j.ejphar.2010.06.016

Lei, X. G., Zhu, J.-H., Cheng, W.-H., Bao, Y., Ho, Y.-S., Reddi, A. R., Holmgren, A., & Arnér, E. S. J. (2016). Paradoxical roles of antioxidant enzymes: Basic mechanisms and health implications. *Physiological Reviews*, *96*(1), 307–364. https://doi.org/10.1152/physrev.00010.2014

Li, Y., Chen, M., Xuan, H., & Hu, F. (2012). Effects of encapsulated propolis on blood glycemic control, lipid metabolism, and insulin resistance in type 2 diabetes mellitus rats. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 1–8. https://doi.org/10.1155/2012/981896

Lima, L. D. C., Andrade, S. P., Campos, P. P., Barcelos, L. S., Soriani, F. M., AL Moura, S., & Ferreira, M. A. N. D. (2014). Brazilian green propolis modulates inflammation, angiogenesis and fibrogenesis in intraperitoneal implant in mice. *BMC Complementary and Alternative Medicine*, *14*(1), 1–9. https://doi.org/10.1186/1472-6882-14-177

Liu, T., Zhang, L., Joo, D., & Sun, S.-C. (2017). NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy*, *2*(1), 1–9. https://doi.org/10.1038/sigtrans.2017.23

Lubberts, E., & van den Berg, W. B. (2013). Cytokines in the pathogenesis of rheumatoid arthritis and collagen-induced arthritis. *Madame Curie bioscience database* (pp. 194–202). Landes Bioscience.

Machado, J. L., Assunção, A. K. M., da Silva, M. C. P., Reis, A. S., Costa, G. C., Arruda, D. S., Rocha, B. A., Vaz, M. M. O. L. L., Paes, A. M. A., Guerra, R. N. M., Berretta, A. A., & Nascimento, F. R. F. (2012). Brazilian green propolis: Anti-inflammatory property by an immunomodulatory activity. *Evidence-Based Complementary and Alternative Medicine*, *2012*, 1741-4288. https://doi.org/10.1155/2012/157652

Mahmoud, A. A., & Ismail, M. A. (2011). Serum protein carbonyl content, total thiol and nitric oxide in patients with rheumatoid arthritis. *Journal of American Science*, *7*, 683–686.

Mirzoeva, O., & Calder, P. J. P. (1996). The effect of propolis and its components on eicosanoid production during the inflammatory response. *Prostaglandins, Leukotrienes and Essential Fatty Acids*, *55*(6), 441–449. https://doi.org/10.1016/S0952-3278(96)90129-5

Missima, F., Pagliarone, A. C., Orsatti, C. L., Araújo, J. P. Jr, & Sforcin, J. M. (2010). The Effect of propolis on Th1/Th2 cytokine expression and production by melanoma-bearing mice submitted to stress. *Phytotherapy Research*, *24*(10), 1501–1507. https://doi.org/10.1002/ptr.3142

Mousa, T. H., Al-Obaidi, Z. M. J., & Alkhafaji, S. L. (2021). Molecular docking studies and evaluation of the anti-inflammatory activity of ibuprofen-tranexamic acid codrug. *Latin American Journal of Pharmacy*, *40*, 128–134.

Mujica, V., Orrego, R., Pérez, J., Romero, P., Ovalle, P., Zúñiga-Hernández, J., Arredondo, M., & Leiva, E. (2017). The role of propolis in oxidative stress and lipid metabolism: A randomized controlled trial. *Evidence-Based Complementary and Alternative Medicine*, *2017*, 4272940. https://doi.org/10.1155/2017/4272940

Munstedt, K., & Zymunt, M. (2001). Propolis-current and future medical uses. *American Bee Journal*, *141*(7), 507–510.

Murata, K., Yatsunami, K., Fukuda, E., Onodera, S., Mizukami, O., Hoshino, G., & Kamei, T. (2004). Antihyperglycemic effects of propolis mixed with mulberry leaf extract on patients with type 2 diabetes. *Alternative Therapies in Health and Medicine*, *10*(3), 78–79.

Myasoedova, E., & Gabriel, S. E. (2010). Cardiovascular disease in rheumatoid arthritis: A step forward. *Current Opinion in Rheumatology*, *22*(3), 342–347. https://doi.org/10.1097/BOR.0b013e3283379b91

Nader, M. A., El-Agamy, D. S., & Suddek, G. M. (2010). Protective effects of propolis and thymoquinone on development of atherosclerosis in cholesterol-fed rabbits. *Archives of Pharmacal Research*, *33*(4), 637–643. https://doi.org/10.1007/s12272-010-0420-1

Nattagh-Eshtivani, E., Jokar, M., Tabesh, H., Nematy, M., Safarian, M., Pahlavani, N., Maddahi, M., & Khosravi, M. (2021). The effect of propolis supplementation on inflammatory factors and oxidative status in women with rheumatoid arthritis: Design and research protocol of a double-blind, randomized controlled. *Contemporary Clinical Trials Communications*, *23*, 100807. https://doi.org/10.1016/j.conctc.2021.100807

Nelson, R. H. (2013). Hyperlipidemia as a risk factor for cardiovascular disease. *Primary Care: Clinics in Office Practice*, *40*(1), 195–211. https://doi.org/10.1016/j.pop.2012.11.003

Newairy, A., & Abdou, H. M. (2013). Effect of propolis consumption on hepatotoxicity and brain damage in male rats exposed to chlorpyrifos. *African Journal of Biotechnology*, *12*(33), 5232–5243.

Nirala, S. K., & Bhadauria, M. (2008). Propolis reverses acetaminophen induced acute hepatorenal alterations: A biochemical and histopathological approach. *Archives of Pharmacal Research*, *31*(4), 451–461. https://doi.org/10.1007/s12272-001-1178-5

Nna, V. U., Bakar, A. B. A., Lazin, M. R. M. L. M., & Mohamed, M. (2018). Antioxidant, anti-inflammatory and synergistic anti-hyperglycemic effects of Malaysian propolis and metformin in streptozotocin–induced diabetic rats. *Food and Chemical Toxicology*, *120*, 305–320. https://doi.org/10.1016/j.fct.2018.07.028

Norata, G. D., Marchesi, P., Passamonti, S., Pirillo, A., Violi, F., & Catapano, A. L. (2007). Anti-inflammatory and anti-atherogenic effects of cathechin, caffeic acid and trans-resveratrol in apolipoprotein E deficient mice. *Atherosclerosis*, *191*(2), 265–271. https://doi.org/10.1016/j.atherosclerosis.2006.05.047

O'Dell, J. R. (2004). Therapeutic strategies for rheumatoid arthritis. *New England Journal of Medicine*, *350*(25), 2591–2602. https://doi.org/10.1056/NEJMra040226

Oršolić, N., Sirovina, D., Končić, M. Z., Lacković, G., Gregorović, G. J. B. C., & Medicine, A. (2012). Effect of Croatian propolis on diabetic nephropathy and liver toxicity in mice. *BMC Complementary and Alternative Medicine*, *12*(1), 117. https://doi.org/10.1186/1472-6882-12-117

Oztürk, H. S., Cimen, M. Y., Cimen, O. B., Kaçmaz, M., & Durak, I. (1999). Oxidant/antioxidant status of plasma samples from patients with rheumatoid arthritis. *Rheumatology International*, *19*(1–2), 35–37. https://doi.org/10.1007/s002960050097

Ozyurt, H., Irmak, M. K., Akyol, O., & Söğüt, S. (2001). Caffeic acid phenethyl ester changes the indices of oxidative stress in serum of rats with renal ischaemia-reperfusion injury. *Cell Biochemistry & Function*, *19*, 259–263.

Pahlavani, N., Malekahmadi, M., Firouzi, S., Rostami, D., Sedaghat, A., Moghaddam, A. B., … Safarian, M. (2020). Molecular and cellular mechanisms of the effects of Propolis in inflammation, oxidative stress and glycemic control in chronic diseases. *Nutrition & Metabolism*, *17*(1), 1–12.

Pahlavani, N., Sedaghat, A., Bagheri Moghaddam, A., Mazloumi Kiapey, S. S., Gholizadeh Navashenaq, J., Jarahi, L., Reazvani, R., Norouzy, A., Nematy, M., Safarian, M., & Ghayour-Mobarhan, M. (2019). Effects of propolis and melatonin on oxidative stress, inflammation, and clinical status in patients with primary sepsis: Study protocol and review on previous studies. *Clinical Nutrition ESPEN*, *33*, 125–131. https://doi.org/10.1016/j.clnesp.2019.06.007

Park, Y.-B., Choi, H. K., Kim, M.-Y., Lee, W.-K., Song, J., Kim, D.-K., & Lee, S.-K. (2002). Effects of antirheumatic therapy on serum lipid levels in patients with rheumatoid arthritis: A prospective study. *The American Journal of Medicine*, *113*(3), 188–193. https://doi.org/10.1016/S0002-9343(02)01186-5

Park, Y. B., Lee, S. K., Lee, W. K., Suh, C. H., Lee, C. W., Lee, C. H., … Lee, J. (1999). Lipid profiles in untreated patients with rheumatoid arthritis. *Journal of Rheumatology*, *26*(8), 1701–1704.

Pascoal, A., Feás, X., Dias, T., Dias, L. G., & Estevinho, L. M. (2014). The role of honey and propolis in the treatment of infected wounds. In K. Kon (Ed.), *Microbiology for surgical infections* (pp. 221–234). Elsevier.

Paulino, N., Abreu, S. R. L., Uto, Y., Koyama, D., Nagasawa, H., Hori, H., Dirsch, V. M., Vollmar, A. M., Scremin, A., & Bretz, W. A. (2008). Anti-inflammatory effects of a bioavailable compound. *Artepillin C, in Brazilian Propolis*, *587*(1–3), 296–301. https://doi.org/10.1016/j.ejphar.2008.02.067

Ramos, A., & Miranda, J. (2007). Propolis: A review of its anti-inflammatory and healing actions. *Journal of Venomous Animals and Toxins Including Tropical Diseases*, *13*(4), 697–710. https://doi.org/10.1590/S1678-91992007000400002

Remirez, D., González, R., Rodriguez, S., Ancheta, O., Bracho, J. C., Rosado, A., Rojas, E., & Ramos, M. E. (1997). Protective effects of Propolis extract on allyl alcohol-induced liver injury in mice. *Phytomedicine*, *4*(4), 309–314. https://doi.org/10.1016/S0944-7113(97)80038-4

Rivera-Yañez, N., Rodriguez-Canales, M., Nieto-Yañez, O., Jimenez-Estrada, M., Ibarra-Barajas, M., Canales-Martinez, M., Medicine,

A. (2018). Hypoglycaemic and antioxidant effects of propolis of chihuahua in a model of experimental diabetes. *Evidence-Based Complementary and Alternative Medicine*, *2018*, 1–10. https://doi.org/10.1155/2018/4360356

Rodriguez, S., Ancheta, O., Ramos, M., Remirez, D., Rojas, E., & Gonzalez, R. (1997). Effects of Cuban red propolis on galactosamine-induced hepatitis in rats. *Pharmacological Research*, *35*(1), 1–4. https://doi.org/10.1006/phrs.1996.9998

Ronda, N., Favari, E., Borghi, M. O., Ingegnoli, F., Gerosa, M., Chighizola, C., Zimetti, F., Adorni, M. P., Bernini, F., & Meroni, P. L. (2014). Impaired serum cholesterol efflux capacity in rheumatoid arthritis and systemic lupus erythematosus. *Annals of the Rheumatic Diseases*, *73*(3), 609–615. https://doi.org/10.1136/annrheumdis-2012-202914

Roy, J., Galano, J. M., Durand, T., Le Guennec, J. Y., & Chung-Yung Lee, J. (2017). Physiological role of reactive oxygen species as promoters of natural defenses. *The FASEB Journal*, *31*(9), 3729–3745. https://doi.org/10.1096/fj.201700170R

Russo, A., Longo, R., & Vanella, A. (2002). Antioxidant activity of propolis: Role of caffeic acid phenethyl ester and galangin. *Fitoterapia*, *73*, S21–S29. https://doi.org/10.1016/S0367-326X(02)00187-9

Sahin, A., Turkmen, S., Guzel, N., Mentese, A., Turedi, S., Karahan, S. C., Yulug, E., Demir, S., Aynaci, O., Deger, O., & Gunduz, A. (2018). A comparison of the effects of grayanotoxin-containing honey (Mad Honey), normal honey, and propolis on fracture healing. *Medical Principles and Practice*, *27*(2), 99–106. https://doi.org/10.1159/000487552

Salehi-Sahlabadi, A., Chhabra, M., Rahmani, J., Momeni, A., Karam, G., Nattagh-Eshtivani, E., Nouri, M., Clark, C., Salehi, P., & Hekmatdoost, A. (2020). The effect of propolis on anthropometric indices and lipid profile: A systematic review and meta-analysis of randomized controlled trials. *Journal of Diabetes & Metabolic Disorders*, *19*(2), 1835–1843. https://doi.org/10.1007/s40200-020-00604-2

Samadi, N., Mozaffari-Khosravi, H., Rahmanian, M., & Askarishahi, M. (2017). Effects of bee propolis supplementation on glycemic control, lipid profile and insulin resistance indices in patients with type 2 diabetes: A randomized, double-blind clinical trial. *Journal of Integrative Medicine*, *15*(2), 124–134. https://doi.org/10.1016/S2095-4964(17)60315-7

Sameni, H. R., Ramhormozi, P., Bandegi, A. R., Taherian, A. A., Mirmohammadkhani, M., & Safari, M. (2016). Effects of ethanol extract of propolis on histopathological changes and anti-oxidant defense of kidney in a rat model for type 1 diabetes mellitus. *Journal of Diabetes Investigation*, *7*(4), 506–513. https://doi.org/10.1111/jdi.12459

Santos, V. R. (2012). *Propolis: Alternative medicine for the treatment of oral microbial diseases* Vol. *7*, (pp. 133–169).

Sarban, S., Kocyigit, A., Yazar, M., & Isikan, U. E. (2005). Plasma total antioxidant capacity, lipid peroxidation, and erythrocyte antioxidant enzyme activities in patients with rheumatoid arthritis and osteoarthritis. *Clinical Biochemistry*, *38*(11), 981–986. https://doi.org/10.1016/j.clinbiochem.2005.08.003

Sarker, K. K., Sethi, J., & Mohanty, U. (2020). Comparative clinical effects of spinal manipulation, core stability exercise, and supervised exercise on pain intensity, segmental instability, and health-related quality of life among patients with chronic nonspecific low back pain: A randomized control trial. *Journal of Natural Science, Biology and Medicine*, *11*(1), 27. https://doi.org/10.4103/jnsbm.JNSBM_101_19

Sato, M., Miyazaki, T., Nagaya, T., Murata, Y., Ida, N., Maeda, K., & Seo, H. (1996). Antioxidants inhibit tumor necrosis factor-alpha mediated stimulation of interleukin-8, monocyte chemoattractant protein-1, and collagenase expression in cultured human synovial cells. *The Journal of Rheumatology*, *23*(3), 432–438.

Scazzocchio, F., D'auria, F., Alessandrini, D., & Pantanella, F. (2006). Multifactorial aspects of antimicrobial activity of propolis. *Microbiological Research*, *161*(4), 327–333. https://doi.org/10.1016/j.micres.2005.12.003

Scheller, S., Wilczok, T., Imielski, S., Krol, W., Gabrys, J., & Shani, J. (1990). Free radical scavenging by ethanol extract of propolis. *International Journal of Radiation Biology*, *57*(3), 461–465. https://doi.org/10.1080/09553009014552601

Scott, D. L., Wolfe, F., & Huizinga, T. W. J. (2010). Rheumatoid arthritis. *Lancet*, *376*, 1094–1108.

Selamoglu-Talas, Z., Ozdemir, I., Ciftci, O., & Cakir, O. (2013). Propolis attenuates oxidative injury in brain and lung of nitric oxide synthase inhibited rats. *Journal of Pharmaceutical Care*, *1*, 45–50.

Seven, I., Aksu, T., & Seven, P. T. (2010). The effects of propolis on biochemical parameters and activity of antioxidant enzymes in broilers exposed to lead-induced oxidative stress. *Asian-Australasian Journal of Animal Sciences*, *23*(11), 1482–1489. https://doi.org/10.5713/ajas.2010.10009

Sforcin, J. M. (2007). Propolis and the immune system: A review. *Journal of Ethnopharmacology*, *113*(1), 1–14. https://doi.org/10.1016/j.jep.2007.05.012

Sforcin, J. M., & Bankova, V. (2011). Propolis: Is there a potential for the development of new drugs? *Journal of Ethnopharmacology*, *133*(2), 253–260. https://doi.org/10.1016/j.jep.2010.10.032

Shi, Y.-Z., Liu, Y.-C., Zheng, Y.-F., Chen, Y.-F., Si, J.-J., Chen, M.-L., Shou, Q.-Y., Zheng, H.-Q., & Hu, F.-L. (2019). Ethanol extract of Chinese propolis attenuates early diabetic retinopathy by protecting the blood–retinal barrier in streptozotocin-induced diabetic rats. *Journal of Food Science*, *84*(2), 358–369. https://doi.org/10.1111/1750-3841.14435

Shinohara, R., Ohta, Y., Hayashi, T., & Ikeno, T. J. P. R. (2002). Evaluation of antilipid peroxidative action of propolis ethanol extract. *Phytotherapy Research*, *16*(4), 340–347. https://doi.org/10.1002/ptr.894

Shukla, S., Bhadauria, M., & Jadon, A. (2004). *Effect of propolis extract on acute carbon tetrachloride induced hepatotoxicity* Vol. *42*, (pp. 993–997). https://pubmed.ncbi.nlm.nih.gov/15511003/

Silva, V., Genta, G., Möller, M. N., Masner, M., Thomson, L., Romero, N., Radi, R., Fernandes, D. C., Laurindo, F. R. M., Heinzen, H., Fierro, W., & Denicola, A. (2011). Antioxidant activity of Uruguayan propolis. In vitro and cellular assays. *Journal of Agriculture and Food Chemistry*, *59*(12), 6430–6437. https://doi.org/10.1021/jf201032y

Sobočanec, S., Šverko, V., Balog, T., Šarić, A., Rusak, G., Likić, S., Kušić, B., Katalinić, V., Radić, S., & Marotti, T. (2006). Oxidant/antioxidant properties of Croatian native propolis. *Journal of Agricultural and Food Chemistry*, *54*(21), 8018–8026. https://doi.org/10.1021/jf0612023

Soleimani, D., Miryan, M., Hadi, V., Gholizadeh Navashenaq, J., Moludi, J., Sayedi, S. M., Bagherniya, M., Askari, G., Nachvak, S. M., Sadeghi, E., Rashidi, A. A., & Hadi, S. (2021). Effect of propolis supplementation on athletic performance, body composition, inflammation, and oxidative stress following intense exercise: A triple-blind randomized clinical trial. *Food Science & Nutrition*, *9*(7), 3631–3640. https://doi.org/10.1002/fsn3.2319

Soromou, L. W., Chu, X., Jiang, L., Wei, M., Huo, M., Chen, N. A., Guan, S., Yang, X., Chen, C., Feng, H., & Deng, X. (2012). In vitro and in vivo protection provided by pinocembrin against lipopolysaccharide-induced inflammatory responses. *International Immunopharmacology*, *14*(1), 66–74. https://doi.org/10.1016/j.intimp.2012.06.009

Stamler, J., Daviglus, M. L., Garside, D. B., Dyer, A. R., Greenland, P., & Neaton, J. D. (2000). Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA*, *284*(3), 311–318. https://doi.org/10.1001/jama.284.3.311

Steinman, L. (2007). A brief history of Th 17, the first major revision in the Th 1/Th 2 hypothesis of T Cell–mediated tissue damage. *Nature Methods*, *13*(2), 139–145.

Su, K.-Y., Hsieh, C.-Y., Chen, Y.-W., Chuang, C.-T., Chen, C.-T., & Chen, Y.-L.-S. (2014). Taiwanese green propolis and propolin G protect the liver from the pathogenesis of fibrosis via eliminating TGF-β-induced Smad2/3 phosphorylation. *Journal of Agricultural and Food Chemistry*, *62*(14), 3192–3201. https://doi.org/10.1021/jf500096c

Sur Arslan, A., & Tatlı Seven, P. (2017). The effects of propolis on serum malondialdehyde, fatty acids and some blood parameters in *Japanese quail* (Coturnix coturnix japonica) under high stocking density. *Journal of Applied Animal Research*, *45*(1), 417–422. https://doi.org/10.1080/09712119.2016.1206901

Surh, Y.-J., Chun, K.-S., Cha, H.-H., Han, S. S., Keum, Y.-S., Park, K.-K., & Lee, S. S. (2001). Molecular mechanisms underlying chemopreventive activities of anti-inflammatory phytochemicals: Down-regulation of COX-2 and iNOS through suppression of NF-κB activation. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *480-481*, 243–268. https://doi.org/10.1016/S0027-5107(01)00183-X

Szliszka, E., Kucharska, A. Z., Sokół-Łętowska, A., Mertas, A., Czuba, Z. P., & Król, W. (2013). Chemical composition and anti-inflammatory effect of ethanolic extract of Brazilian green propolis on activated J774A.1 macrophages. *Evidence-Based Complementary and Alternative Medicine*, *2013*, 1–13. https://doi.org/10.1155/2013/976415

Tanaka, M., Okamoto, Y., Fukui, T., & Masuzawa, T. (2012). Suppression of interleukin 17 production by Brazilian propolis in mice with collagen-induced arthritis. *Inflammopharmacology*, *20*(1), 19–26. https://doi.org/10.1007/s10787-011-0088-2

Tan-no, K., Nakajima, T., Shoji, T., Nakagawasai, O., Niijima, F., Ishikawa, M., Endo, Y., Sato, T., Satoh, S., & Tadano, T. (2006). Anti-inflammatory effect of propolis through inhibition of nitric oxide production on carrageenin-induced mouse paw edema. *Biological and Pharmaceutical Bulletin*, *29*(1), 96–99. https://doi.org/10.1248/bpb.29.96

Tao, Y., Xie, S., Xu, F., Liu, A., Wang, Y., Chen, D., Pan, Y., Huang, L., Peng, D., Wang, X. U., & Yuan, Z. (2018). Ochratoxin A: Toxicity, oxidative stress and metabolism. *Food and Chemical Toxicology*, *112*, 320–331. https://doi.org/10.1016/j.fct.2018.01.002

Taysi, S., Polat, F., Gul, M., Sari, R., & Bakan, E. (2002). Lipid peroxidation, some extracellular antioxidants, and antioxidant enzymes in serum of patients with rheumatoid arthritis. *Rheumatology International*, *21*(5), 200–204. https://doi.org/10.1007/s00296-001-0163-x

Tehrani, H. S., & Moosavi-Movahedi, A. A. (2018). Catalase and its mysteries. *Progress in Biophysics and Molecular Biology*, *140*, 5–12. https://doi.org/10.1016/j.pbiomolbio.2018.03.001

Tietge, U. J. (2014). Hyperlipidemia and cardiovascular disease: Inflammation, dyslipidemia, and atherosclerosis. *Current Opinion in Lipidology*, *25*(1), 94–95. https://doi.org/10.1097/MOL.0000000000000051

Tobón, G. J., Youinou, P., & Saraux, A. (2010). The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. *Autoimmunity Reviews*, *9*(5), A288–A292. https://doi.org/10.1016/j.autrev.2009.11.019

Tolba, M. F., Azab, S. S., Khalifa, A. E., Abdel-Rahman, S. Z., & Abdel-Naim, A. B. (2013). Caffeic acid phenethyl ester, a promising component of propolis with a plethora of biological activities: A review on its anti-inflammatory, neuroprotective, hepatoprotective, and cardioprotective effects. *IUBMB Life*, *65*(8), 699–709. https://doi.org/10.1002/iub.1189

Torel, J., Cillard, J., & Cillard, P. (1986). Antioxidant activity of flavonoids and reactivity with peroxy radical. *Phytochemistry*, *25*(2), 383–385. https://doi.org/10.1016/S0031-9422(00)85485-0

Uzel, A., Sorkun, K., Önçağ, Ö., Çoğulu, D., Gençay, Ö., & Sali˙h, B. (2005). Chemical compositions and antimicrobial activities of four different Anatolian propolis samples. *Microbiological Research*, *160*(2), 189–195. https://doi.org/10.1016/j.micres.2005.01.002

Vaghef-Mehrabany, E., Homayouni-Rad, A., Alipour, B., Sharif, S.-K., Vaghef-Mehrabany, L., & Alipour-Ajiry, S. (2016). Effects of probiotic supplementation on oxidative stress indices in women with rheumatoid arthritis: A randomized double-blind clinical trial. *Journal of the American College of Nutrition*, *35*(4), 291–299. https://doi.org/10.1080/07315724.2014.959208

Van Den Berg, W. B., & Miossec, P. J. N. R. R. (2009). IL-17 as a future therapeutic target for rheumatoid arthritis. *Nature Reviews Rheumatology*, *5*(10), 549–553. https://doi.org/10.1038/nrrheum.2009.179

Wang, K., Jin, X., Li, Q., Sawaya, A., Le Leu, R., Conlon, M., … Hu, F. (2018). Propolis from different geographic origins suppress intestinal inflammation in a model of dss-induced colitis is associated with decreased *Bacteroides* spp. in the gut. *Molecular Nutrition & Food Research*, *62*(17), e1800080. https://doi.org/10.1002/mnfr.201800080

Wang, X., Fang, G., Yang, Y., & Pang, Y. (2019). The newly discovered natural compounds against rheumatoid arthritis-an overview. *Phytochemistry Letters*, *34*, 50–58. https://doi.org/10.1016/j.phytol.2019.09.011

Weinblatt, M. E., Kremer, J. M., Bankhurst, A. D., Bulpitt, K. J., Fleischmann, R. M., Fox, R. I., … Burge, D. J. (1999). A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *New England Journal of Medicine*, *340*(4), 253–259.

Wolska, K., Gorska, A., Antosik, K., & Lugowska, K. (2019). Immunomodulatory effects of propolis and its components on basic immune cell functions. *Indian Journal of Pharmaceutical Sciences*, *81*(4), 575–588. https://doi.org/10.36468/pharmaceutical-sciences.548

Woo, K. J., Jeong, Y.-J., Inoue, H., Park, J.-W., & Kwon, T. K. (2005). Chrysin suppresses lipopolysaccharide-induced cyclooxygenase-2 expression through the inhibition of nuclear factor for IL-6 (NF-IL6) DNA-binding activity. *FEBS Letters*, *579*(3), 705–711. https://doi.org/10.1016/j.febslet.2004.12.048

Xie, Q., Kashiwabara, Y., & Nathan, C. (1994). Role of transcription factor NF-kappa B/Rel in induction of nitric oxide synthase. *Journal of Biological Chemistry*, *269*(7), 4705–4708. https://doi.org/10.1016/S0021-9258(17)37600-7

Yaykasli, K. (2013). Rheumatoid arthritis and adipokines. *European Journal of Basic Medical Sciences*, *3*(2), 38–43. https://doi.org/10.21601/ejbms/9200

Ying-Hua, L., Wei, Z., & Fu-Liang, H. (2012). Progress on anti-inflammatory effects and mechanism of propolis. *Natural Product Research and Development*, *24*(6), 856–859.

Yonar, M. E., Yonar, S. M., & Silici, S. (2011). Protective effect of propolis against oxidative stress and immunosuppression induced by oxytetracycline in rainbow trout (*Oncorhynchus mykiss*, W.). *Fish and Shellfish Immunology*, *31*(2), 318–325.

Yousef, M. I., Salama, A. F. J. F., & Toxicology, C. (2009). Propolis protection from reproductive toxicity caused by aluminium chloride in male rats. *Food and Chemical Toxicology*, *47*(6), 1168–1175. https://doi.org/10.1016/j.fct.2009.02.006

Zakerkish, M., Jenabi, M., Zaeemzadeh, N., Hemmati, A. A., & Neisi, N. (2019). The effect of Iranian propolis on glucose metabolism, lipid profile, insulin resistance, renal function and inflammatory biomarkers in patients with type 2 diabetes mellitus: A randomized double-blind clinical trial. *Scientific Reports*, *9*(1), 7289. https://doi.org/10.1038/s41598-019-43838-8

Zhang, X., Wang, G., Gurley, E. C., & Zhou, H. (2014). Flavonoid apigenin inhibits lipopolysaccharide-induced inflammatory response through multiple mechanisms in macrophages. *PLoS One*, *9*(9), e107072. https://doi.org/10.1371/journal.pone.0107072

Zhao, J.-Q., Wen, Y.-F., Bhadauria, M., Nirala, S. K., Sharma, A., Shrivastava, S., … Mathur, R. (2009). *Protective effects of propolis on* *inorganic mercury induced oxidative stress in mice* Vol. *47*, (pp. 264–269). https://pubmed.ncbi.nlm.nih.gov/19382722/

Zhao, L., Pu, L., Wei, J., Li, J., Wu, J., Xin, Z., Gao, W., & Guo, C. (2016). Brazilian green propolis improves antioxidant function in patients with type 2 diabetes mellitus. *International Journal of Environmental Research and Public Health*, *13*(5), 498. https://doi.org/10.3390/ijerph13050498

Zhu, A., Wu, Z., Zhong, X., Ni, J., Li, Y., Meng, J., Du, C., Zhao, X., Nakanishi, H., & Wu, S. (2018). Brazilian green propolis prevents cognitive decline into mild cognitive impairment in elderly people living at high altitude. *Journal of Alzheimer's Disease*, *63*(2), 551–560. https://doi.org/10.3233/JAD-170630

Zhu, W., Chen, M., Shou, Q., Li, Y., Hu, F.-J.-E.-B.-C., & Medicine, A. (2011). Biological activities of Chinese propolis and Brazilian propolis on streptozotocin-induced type 1 diabetes mellitus in rats. *Evidence-Based Complementary and Alternative Medicine*, *2011*, 1–8. https://doi.org/10.1093/ecam/neq025

Zhu, W., Li, Y.-H., Chen, M.-L., & Hu, F.-L. (2011). Protective effects of Chinese and Brazilian propolis treatment against hepatorenal lesion in diabetic rats. *Human & Experimental Toxicology*, *30*(9), 1246–1255. https://doi.org/10.1177/0960327110387456

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