The roles of strawberry and honey phytochemicals on human health: A possible clue on the molecular mechanisms involved in the prevention of oxidative stress and inflammation

The roles of strawberry and honey phytochemicals on human health: a possible clue on the molecular mechanisms involved in the prevention of oxidative stress and inflammation

Maurizio Battino[a,b,c#,*], Francesca Giampieri[a,c,#], Danila Cianciosi[c], Johura Ansary[c], Xiumen Chen[b], Di Zhang[b,d], Emilio Gil[a], Tamara Forbes-Hernández[a,**]

[a] *Nutrition and Food Science Group, Department of Analytical and Food Chemistry, CITACA, CACTI, University of Vigo - Vigo Campus, Vigo, Spain*

[b] *International Research Center for Food Nutrition and Safety, Jiangsu University, Zhenjiang 212013, China*

[c] *Department of Clinical Sciences, Faculty of Medicine, Polytechnic University of Marche, Ancona, Italy.*

[d] *Jiangsu Hengshun Group Co., Ltd., Zhenjiang 212000, China.*

[#]These authors contributed equally to this work.

*Correspondence to: *Prof. Maurizio Battino, Dipartimento di Scienze Cliniche Specialistiche ed Odontostomatologiche (DISCO)-Sez. Biochimica, Facoltà di Medicina, Università Politecnica delle Marche, Ancona, Via Ranieri 65, 60131, Italy. E mail: m.a.battino@univpm.it; Tel.: +39-071-220-4646; Fax: +39-071-220-4123.*

**Correspondence to: *Dr. Tamara Yuliett Forbes-Hernandez, Nutrition and Food Science Group, Department of Analytical and Food Chemistry, CITACA, CACTI, University of Vigo - Vigo Campus, Vigo, Spain.* E mail: tamara.forbe@gmail.com; Tel.: +39-071-220-4646; Fax: +39-071-220-4123.

Abstract

Background

Oxidative stress and inflammation contribute to the etiopathogenesis of several human chronic diseases, such as cancer, diabetes, cardiovascular diseases and metabolic syndrome. Besides classic stimuli, such as reactive oxidant species, endotoxins (i.e., bacteria lipopolysaccharide), cytokines or carcinogens, oxidative stress and inflammation can be triggered by a poor diet and an excess of body fat and energy intake. Strawberry and honey are common rich sources of nutrients and bioactive compounds, widely studied for their roles exerted in health maintenance and disease prevention.

Purpose

This review aims to summarize and update the effects of strawberry and honey against oxidative stress and inflammation, with emphasis on metabolism and on the main molecular mechanisms involved in these effects.

Methods

A wide range of literature, published in the last 10 years, elucidating the effects of strawberry and honey in preventing oxidative stress and inflammation both *in vitro* (whole matrix and digested fractions) and *in vivo* was collected from online electronic databases (PubMed, Scopus and Web of Science) and reviewed.

Results

Strawberry and honey polyphenols may potentially prevent the chronic diseases related to oxidative stress and inflammation. Several *in vitro* and *in vivo* studies reported the effects of these foods in suppressing the oxidative stress, by decreasing ROS production and oxidative biomarkers, restoring the antioxidant enzyme activities, ameliorating the mitochondrial antioxidant status and

functionality, among others, and the inflammatory process, by modulating the mediators of acute and chronic inflammation essential for the onset of several human diseases. These beneficial properties are mediated in part through their ability to target multiple signaling pathways, such as p38 MAPK, AMPK, PI3K/Akt, NF-κB and Nrf2.

Conclusions

Available scientific literature show that strawberry and honey may be effective in preventing oxidative stress and inflammation. The deep evaluation of the factors that affect their metabolism as well as the assessment of the main molecular mechanisms involved are of extreme importance for the possible therapeutic and preventive benefit against the most common human diseases. However, published literature is still scarce so that deeper studies should be performed in order to evaluate the bioavailability of these food matrices and their effects after digestion.

Keywords: honey; strawberry; polyphenols; bioavailability; oxidative stress; inflammation.

Abbreviation

AAPH, 2,2'-Azobis(2-amidinopropane) dihydrochloride; AMPK, AMP-activated protein kinase; AP-1, activator protein-1; CBG, β-glucosidase; CDs, cyclodextrins; CO2, Carbon dioxide; COX, cyclooxygenase; CRP, C-reactive protein; ECM, extracellular matrix; EGCG, epillocatechin gallate; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinases; GI, gastrointestinal; GPx, glutathione peroxidase; GSH, glutathione; GST, glutathione transferase; HDF, human dermal fibroblasts; HMGB1, High mobility group box-1; HO-1, heme oxygenase-1; IFN, interferon; IL, interleukin; iNOS, inducible NOS; JNK, c-Jun N-terminal kinase; LPH, lactase phlorizin hydrolase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, chemoattractant protein-1; MDA, malondialdehyde; METC, mitochondrial electron transport chain; MIP, macrophage inflammatory proteins; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP, Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing protein 3; NO, nitric oxide; NOS, Nitric oxide synthase; NOXs, NADPH oxidases; Nrf2, nuclear factor erythroid 2–related factor 2; ox-LDL, oxidize low-density lipoprotein; p38, mitogen-activated protein kinases; PGE2, prostaglandin E2; PI3K, Phosphoinositide 3-Kinase; pIKBα, phospho-inhibitory subunit of NF-kBα; PKCδ, Protein kinase C delta type; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; TGF, tumor growth factor; TLR4, toll-like receptor-4; TNF-α, Tumor necrosis factor-α; TPA, 2-O-tetradecanoylphorbol 13-acetate; TRX , Thioredoxin; TXNIP, Thioredoxin-interacting protein; UVA, Ultraviolet A; XDH, xanthine dehydrogenase.

Introduction

A moderate production of free radicals and inflammation is essential for maintaining human well-being and preventing the onset of chronic-degenerative diseases. On one side, under physiological conditions, free radicals, as well as reactive oxygen species (ROS) and reactive nitrogen species (RNS), are essential for regulating, within certain limits, many molecular pathways involved in several biological processes, such as metabolism, differentiation, iron homeostasis, survival and proliferation (Trachootham et al., 2008; Ray et al., 2012). On the other side, inflammation represents the first, adaptive and protective response of the innate immune system to different type of pathogens and injury stimuli, with the aim of re-establishing the homeostasis of damaged tissue (Goldszmid and Trinchieri, 2012; Mihai et al., 2018). The appropriate regulation of this mechanism is indispensable for avoiding the uncontrolled amplification of inflammation and for preventing the shift from the normal tissue repair toward the collateral damage and disease onset (Goldszmid and Trinchieri, 2012). When an excessive production of free radicals occurs, a condition of oxidative stress and a subsequent perpetuation of inflammation results. Oxidative stress can be due to an increase of free radical production and/or a decrease in antioxidant defence: if ROS and RNS are inadequately controlled by cellular antioxidants, they can damage cell and tissue at different site targets (i.e., DNA, proteins and lipids), promoting cell death, through the activation of apoptosis and necrosis, and extracellular matrix (ECM) breakdown. Damaged ECM and necrotic cells in turn release several extracellular and intracellular factors that hyperactivate the inflammatory cascade, leading to an increase in free radical production and oxidative stress in a vicious circle (Raucci et al., 2019; Shah et al., 2019).

In the last decade, several epidemiological studies have demonstrated that the consumption of food enriched in antioxidants and bioactive compounds, able to counteract oxidative stress and inflammation, may represent a strategic tool to maintain health and wellness and to prevent disease onset and progression (Giampieri et al., 2017a). Strawberry and honey are common food of Mediterranean area, with well-established antioxidant and anti-inflammatory activities, whose

consumption has been associated with a lower risk of chronic-degenerative diseases (Afrin et al., 2016, 2018a; Giampieri et al., 2017a; Cianciosi et al., 2018). The aim of the present review is to summarize scientific evidence, obtained from *in vitro* and *in vivo* studies during the last 10 years, on the antioxidant and anti-inflammatory potential of strawberry and honey bioactive compounds in the prevention of the most common pathologies, with particular attention to their metabolism and bioavailability.

Cross talk between oxidative stress and inflammation in health and disease

Oxidative stress and inflammation are intrinsically linked in pathophysiological events where redox imbalance occurs, due to the disruption of redox homeostasis by an imbalance between reductants and oxidants (Fig. 1) (Gill et al., 2010; Shao et al., 2012; Ruiz et al., 2013).

The main cellular sources of ROS are nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidases (NOXs) and mitochondria, throughout the mitochondrial electron transport chain (METC) (Dunn et al., 2015), while the main factors that promote chronic inflammation are excessive production of oxidative stress, proinflammatory cytokines, altered metabolism of adipose tissue and chronic infections (Mihai et al., 2018). During inflammation, $O2^{\cdot -}$ is formed by xanthine dehydrogenase, during METC, in the endoplasmic reticulum (ER), or from different NOXs by enzymatic pathways and uncoupled nitric oxide synthase (NOS), while nitric oxide ($NO^{\bullet}$) is produced from l-arginine and molecular oxygen (O_2) by the activity of various NOS; simultaneous generation of $NO^{\bullet}$ and $O_2^{\bullet -}$ immediately produces peroxynitrite (NO^{-}_3) (Lugrin et al., 2014), which sustains the production of ROS (Forstermann and Li, 2011).

Oxidative stress induces various modifications in lipids, generating several oxidized-specific products, which in turn trigger innate immune responses and stimulate inflammation (Fig. 1) (Parra-Ortiz et al., 2019), such as oxidized cholesteryl-esters that are able to activate macrophages through toll-like receptor-4 (TLR4) and spleen tyrosine kinase, (Choi et al., 2017), or oxidized low-density lipoprotein (ox-LDL), a well-known crucial mediator of inflammation (Lugrin et al., 2014; Chen et

al., 2019). Also metabolic and bioenergetic alterations may modulate macrophages activities, promoting an increase in tissue phospholipid oxidation (Serbulea et al., 2018) and a consequent modification of membrane properties, as well as a stimulation of inflammation (Parra-Ortiz et al., 2019). Besides this, tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and other proinflammatory molecules, such as cyclooxygenase (COX)-2, NOS, superoxide, ROS and NO, are secreted from activated macrophages that may damage DNA by oxidation (Włodarczyk and Nowicka, 2019). In addition, ROS generation in adipocytes stimulates pro-inflammatory adipokines and perpetuates chronic inflammation in the target tissue (Fig. 1) (Parra-Ortiz et al., 2019).

Regarding molecular mechanisms, ROS have a fundamental role in the pro-inflammatory responses through the activation of redox sensitive transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein-1 (AP-1), and their upregulating kinases, including mitogen-activated protein kinases (MAPKs), such as mitogen-activated protein kinases (p38), extracellular signal-regulated kinases (ERK) and c-Jun N-terminal kinase (JNK), as well as posphoinositide 3-Kinase (PI3K) (Fig. 1). Numerous data have indicated a positive feedback between NF-κB activation and inflammatory status, such as the up-regulation of COX-2 and NOS (Kim et al., 2011), inflammatory cytokines, such as TNF-α, IL-1β, IL-2, IL-6, and IL-12 and chemokines (Chen et al., 2018a). The secreted cytokines (i.e., TNF-α, IL-6, IL-1β) recruit the macrophages and neutrophils to the inflammation site, thus reinforcing the inflammatory process and the production of free radicals by macrophages and neutrophils (Cezar et al., 2019). IL-6 and TNF-α can be activated by NF-κB and can further promote NF-κB activation; additionally, TNF-α also stimulates p53 via JNK pathway which are members of the MAPK family and promote apoptosis (Fig. 1) (Quan et al., 2011).

Moreover, increased ROS production is responsible for the mitochondria and ER dysfunction, that activates apoptosis and necrosis. Necrotic tissues are liable for inflammation through the release of high mobility group box-1 (HMGB1) via different receptors of TLR4-dependent pathway and generate a variety of cellular responses, e.g. NF-κB signaling activation (Raucci et al., 2019; Shah

et al., 2019). Furthermore, HMGB1 are responsible for the activation of Nucleotide-binding oligomerization domain, Leucine rich Repeat and Pyrin domain containing protein (NLRP) 3 inflammasome (Duan et al., 2019), together with other activators, such as extracellular ATP and NOX, potassium efflux, phagolysosomes disruption, phagocytosis, and Cathepsin B, which increase ROS production and spark inflammasome-activating signals, as PI3K, thioredoxin (TRX) and thioredoxin-interacting protein (TXNIP). After that, oxidized TRX and TXNIP bind to NLRP3/NALP3, increasing the agglomeration of inflammasome (Martinon, 2010). Activated NLRP3 inflammasome is also responsible for cellular homeostasis disturbance that promotes chronic inflammation by altering the inactive form of the pro-inflammatory cytokine interleukin-1β (pro-IL-1β) into its active form (IL-1β) (Dunn et al., 2015), which increases protein kinase C delta type (PKCδ) activity through C-Jun kinase signaling pathway and promotes ROS production (Ginnan et al., 2013). In addition, nuclear factor erythroid 2–related factor 2 (Nrf2) also contributes to NLRP3 activation, upregulates heme oxygenase-1 (HO-1) (Jhang et al., 2015) and down-regulates expression of TXNIP in autophagy and in mitochondrial biogenesis (Dunn et al., 2015). Interestingly, Nrf2 plays a crucial role against oxidative stress (Jhang et al., 2015) by downregulating inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Chen et al., 2018a) and inhibiting NF-κB signaling pathway and *vice versa* (Khurana et al., 2018).

Metabolism and bioavailability of dietary polyphenols

General aspects

The role of polyphenols in the prevention and/or treatment of several chronic diseases has been emphasized in the last years (Chen et al., 2018b; Cao et al., 2019; Zhao et al., 2019a). The health benefits of these compounds range from antioxidant and free radicals scavenging effects to anti-inflammatory, anticarcinogenic or cardioprotective properties. However, it is known that they are poorly absorbed and/or extensively metabolized by phase I/II enzymatic reactions reaching the target organs in very small concentrations (Brglez Mojzer et al., 2016; Santhakumar et al., 2018;

196 Zhao et al., 2019b). In addition, phenolic compounds undergo numerous transformations to a wide
197 range of new chemical structures before reaching their site of action, and these modifications may
198 significantly affect their health effects (Santhakumar et al., 2018; Zhao et al., 2019b). Hence, the
199 biological activities of polyphenols cannot be fully discussed until the bioavailability issue is
200 addressed. For this reason, in the last decades the bioavailability of dietary polyphenols and derivate
201 metabolites has become a topic of growing interest within the scientific community.
202 From a nutritional point of view, bioavailability can be defined as the fraction of a certain nutrient
203 that is absorbed, retained and finally available for the physiological functions to which it is
204 destined. It refers to as the rate and extent to which the active ingredient is absorbed and becomes
205 available at the site of action. For dietary polyphenols, this definition is usually understood as the
206 partial amount that reaches the bloodstream (Teng and Chen, 2019).
207 Most polyphenols are present in their glycosylated forms (flavan-3-ols are an exception), where one
208 or more sugar residues are bound to a hydroxyl group at C-3 position or the aromatic ring
209 (Giampieri et al., 2017a; Cianciosi et al., 2018). The basic structure of the aglycon and the type of
210 conjugated sugar residue strongly affect their bioavailability (Brglez Mojzer et al., 2016; Murota et
211 al., 2018). Following ingestion, dietary polyphenols are metabolized by the same detoxification
212 pathways described for drugs and xenobiotics (Fig. 2). Although they can experience some primary
213 alterations in the mouth, the most important biotransformations start in the gastrointestinal (GI) tract
214 (Santhakumar et al., 2018; Kawabata et al., 2019). In the small intestine, sugar moieties of the O-
215 glycosides flavonoids are cleaved from the phenolic backbone through β-hydrolysis. This step is
216 primarily mediated by the lactase phlorizin hydrolase (LPH) and the β-glucosidase (CBG) enzymes,
217 which act in the brush border of the small intestine epithelial cells or in cytosol, respectively. The
218 resulting aglycones are capable to cross the enteric barrier by passive diffusion due to their
219 increased lipophilicity and proximity to the cellular membrane for further distribution to tissues and
220 finally excretion in urine (Marín et al., 2015; Santhakumar et al., 2018; Teng and Chen, 2019).

Other families of dietary polyphenols such flavan-3-ols, which are not glycosylated but often acylated, are absorbed at enterocyte level without suffering any hydrolysis or deconjugation. Likewise, some hydroxycinnamic acids or flavonoids associated to a rhamnose moiety, are resistant to the LPH or CBG action and consequently not absorbed in the small intestine. In these cases, they need to reach the colon and subsequently be metabolized by the colonic microbiota, leading to the production of various hydroxyphenylacetic acids (Marín et al., 2015).

Once absorbed by the intestinal epithelium and before passive transport into the systemic circulation, polyphenols derivatives or aglycones undergo some phase II enzymatic reactions including sulfation, glucuronidation, or methylation by the action of sulfotransferases, uridine–5-diphosphate glucuronosyltransferases and catechol-O-methyltransferases, respectively. The resulting products enter in the bloodstream and rapidly reach the liver, where they can be subjected to additional conjugation reactions, and transported to the bloodstream again until they are eliminated in the urine or efflux back into the lumen as bile components (Marín et al., 2015; Kawabata et al., 2019; Teng and Chen, 2019). All these conjugation reactions are greatly efficient, so that plasma concentrations of free aglycones are very low after nutritional doses.

The conjugated forms that return into the intestine, together with the remaining unmodified polyphenols (generally, multimeric polyphenols), are metabolized by gut microbial enzymes before being reabsorbed again. Such enterohepatic circulation contributes to increase the level and the half-life of flavonoids in the plasma (Murota et al., 2018). It has been estimated that approximately 90-95% of the dietary polyphenols are not absorbed in the small intestine and pass directly to the colon (Olivero-David et al., 2019). Finally, the metabolites that are not absorbed are eliminated via feces (Marín et al., 2015; Santhakumar et al., 2018; Kawabata et al., 2019) (Fig. 2).

Strawberry and honey polyphenols

Since the knowledge on the absorption and metabolism of strawberry and honey has been recently described in our previous works (Afrin et al., 2016, 2019), here it will be discussed only in brief.

In strawberry the main classes of polyphenols are anthocyanins, ellagitannins and phenolic acids. After ingestion, a small part of anthocyanins is absorbed from the stomach through the activity of a bilitranslocase and reach the liver where they may enter the systemic circulation or can be carried back to the intestine through the bile. The remained anthocyanins, that are not absorbed from the stomach, reach the small and large intestine, where they are converted in many metabolites, such as quinonoids, chalcones and hemiketals, that in turn are absorbed in the jejunum and are subjected to several conjugation reactions in liver, intestine and kidney.

In humans the bioavailability of strawberry anthocyanins is in general very low, being less than 2% of the total anthocyanins ingested (Ariza et al., 2018). In plasma and urine of volunteers consuming from 100 to 400 g of fresh or stored strawberries, more than 80% of pelargonidin-derived compounds were detected, being pelargonidin-O-glucuronide the main one, followed by small amounts of pelargonidin aglycone and pelargonidin-O-sulfate. In addition, these compounds were detected in plasma after 8 h from strawberry consumption, while in urine in a period of 2 h; after 24 h the excreted amount was on an average 0.9% of the ingested dose (Felgines et al., 2003; Carkeet et al., 2008; Hollands et al., 2008; Mullen et al., 2008; Azzini et al., 2010).

Another important class of polyphenols in strawberry are ellagitannins. After ingestion, these compounds are in part absorbed in the jejunum, after hydrolyzing to ellagic acid (EA), due to the neutral pH environment; EA is then transported into the enterocytes where it is methylated, glucorinated and subjected to hepatic phase II biotransformations, originating a complex variety of conjugated metabolites. However, most of ellagitannins and EA, that are not absorbed in the intestine, are transformed by gut microbiota into urolithins, the most known ellagitannins metabolites, that are subjected to phase II biotransformations in the hepatocyte and enterocyte, originating urolithinmetabolites. Regarding the bioavailability of ellagitannins, two studies showed that after consuming different type of food containing ellagitannin, including strawberry, urolithin A, B and glucuronic acid were detected in urine, while neither ellagitannins nor EA were identified (Cerdá et al., 2005; Truchado et al., 2012).

Phenolic acids in general are not absorbed in the intestine and reach the colon, where they can be modified by microbiota, absorbed, subjected to metabolism in the liver and then excreted in urine. Only one study has assessed the bioavailability of strawberry phenolic acids in humans: after consuming 750 g of this fruit, benzoic acids (i.e., syringic, hydroxybenzoic, protocatechuic and gentistic acids) were detected in urine within 5 h, while cinnamic acids were detected only in trace (Russell et al., 2009).

Regarding honey, the main class of polyphenols of this matrix are flavonoids, that are present mainly as aglycones, because of the presence of some glucosidases deriving from the salivary glands of bees, which contribute to hydrolyze these compounds, increasing their bioavailability. Once absorbed from the intestinal epithelium, these compounds are subjected to the second phase of the metabolism, that gives rise to many metabolites, such as sulfonated-, gluconated and methylated products by different types of enzymes, including sulfotransferases, glucuronosyltransferases and methyltransferases. These metabolites enter the third phase of the metabolism, where some proteins associated with multi-resistance (MRP1, MRP2, MRP3) transport flavonoids back into the intestinal lumen, inside the blood cells or in the hepatocytes through the portal venous system. Finally, the glycosided flavonoids, that are resistant to LPH or CBG action, are not absorbed from the small intestine, but are deglycosylated by the microbiota of colon into different derivates that can be absorbed by the liver and be further conjugated or can be excreted with the feces. To the best of our knowledge, only one study has evaluated the bioavailability of honey in humans: in plasma of 40 healthy volunteers consuming 1.5 mg/kg of buckwheat honey, the total antioxidant capacity and the total phenolic content increased 2 h after honey supplementation and remained high for 6 h, suggesting that the bioavailability of these phenolic compounds is rather high (Schramm et al., 2003).

Factors that impact dietary polyphenols bioavailability

Some physicochemical properties of dietary polyphenols, such as solubility, stability under GI tract conditions (pH variations, enzymes, presence or absence of other nutrients) and gastric residence time, together with the characteristics of the food matrix and microbiota individualities, determine to a large extent of the bioavailability of these compounds.

Structure and stability

Chemical structure of polyphenols is a critical factor affecting their bioavailability. In food matrices, they can be found as glycosylated forms, aglycones or polymers (Olivero-David et al., 2019). The hydroxylation degree, methoxylation, as well as the hydrogenation of the double bond between C2 and C3, significantly influence the stability of flavonoids, the main family of dietary polyphenols. The stability of non-flavonoid polyphenols is also influenced by the hydroxylation degree (Luca et al., 2019).

As explained above, most dietary polyphenols cannot be absorbed in their native form and experience a series of transformations by intestinal enzymes or colonic microbiota (Olivero-David et al., 2019). Polymerization degree significantly influences the cellular uptake of polyphenols (Hu et al., 2017): for example, polymeric compounds, such as proanthocyanidins that are typical phenols of strawberry, have greater difficulty for being absorbed in the small intestine and are poorly degraded by the colonic microbiota due to the complexity of their structure (Olivero-David et al., 2019). In that sense, it has been shown that absorption of dimers of procyanidins is much lower (<1%) than absorption of monomers as epicatechin, which is around 45% (Hu et al., 2017).

The most absorbed polyphenols are isoflavones along with gallic acid, followed by flavanones, catechins and quercetin glycosides. On the contrary, anthocyanins and proanthocyanidins are the least absorbed. The passage across the lipid moiety of the membrane also depends on polyphenol spatial distribution, in which flatness is preferred (Brglez Mojzer et al., 2016).

Regarding the stability, the gastric acid conditions (pH range between 2-4) favor polyphenols stability, while the alkaline conditions of the intestine (up to pH~7.4) contribute to their degradation (Hu et al., 2017; Squillaro et al., 2018), leading to a low overall uptake into bloodstream (Hu et al., 2017).

Solubility

Solubility is an essential physicochemical property that also impacts polyphenols bioavailability. Chemically, polyphenols can be considered amphiphilic molecules, which means that they possess both hydrophilic (polar) and lipophilic (apolar) properties. The presence of hydroxyl groups contributes to their hydrophilicity, while phenyl rings contribute to the hydrophobicity (Brglez Mojzer et al., 2016; Zhao et al., 2019b).

It could be thought that polyphenols with greater solubility would have a higher bioavailability, however, this idea is not completely true, since it underestimates the important role of intestinal cell membrane permeability. According to their solubility and cell membrane permeability, dietary polyphenols can be classified into three main categories: (i) high solubility with poor cell membrane permeability; (ii) low solubility and poor cell membrane permeability; and (iii) low solubility with high cell membrane permeability (Hu et al., 2017; Squillaro et al., 2018). It is accepted that the best absorbed compounds by the biological systems are those that dissolve well in the two phases, that means compounds with a lipid/H_2O partition coefficient approximate or equal to 1, because they can pass from the external medium to the membrane and from this to the internal aqueous cell medium.

Effects of food matrices

Most polyphenolic compounds are released from food matrices during the gastric phase of digestion. The combination of a low pH with the action of pepsin and peristaltic movements favor this process and lead to a diminution in the particles size leading to a major absorption. Likewise,

bile and pancreas secretions, such as amylase, phospholipase, trypsinogen and chymotrypsinogen, lipase, sterol esterase and bile salts, contribute to the formation of water-soluble mixed micelles (Hu et al., 2017). Polyphenols with higher solubility are easily released from dietary matrices, while hydrophobic compounds tend to interact with other food components that decrease or delay their absorption (Zhao et al., 2019b).

Some food components or combinations of them may facilitate or inhibit the bioavailability of polyphenols. For example, consumption of ice cream in combination with berry juice markedly reduced the recovery of total anthocyanins (Hu et al., 2017).

Interactions with gut microbiota

Microbial degradation is an important factor influencing bioavailability of dietary polyphenols (Liu et al., 2018). Approximately 90% of consumed polyphenols reach the colon and are transformed into bioavailable products by the resident microbiota (Pasinetti et al., 2018). The gut microbiota - defined as diverse bacteria that form symbiotic relationships with their hosts- is responsible for numerous biotransformation of phenolic compounds thanks to the action of several enzymes, including glucuronidases, glycosidases, amidases, sulfatases, and esterases. This enzymatic diversity allows the rupture of complex structures of polyphenols into different metabolites with low molecular weight, which are more easily absorbable (Murota et al., 2018; Santhakumar et al., 2018).

Some factors such as subject health status, diet, exposure to pharmacological therapies, psychological and physiological stress as well as interactions with the environment can alter the composition of the intestinal microbiota. Thus, each subject possesses a unique combination of these microorganisms. However, although this great diversity, some studies agree that healthy gut microbiota is composed of a high proportion of metabolically-active bacteria, including the *Bifidobacterium spp*., *Eubacterium spp*. and *Ruminococcus spp*., a low proportion of the phyla Firmicutes and Bacteriodetes, and a reduced ratio of inflammatory pathogens including the

Proteobacteria. Each of these bacterial species presents specific catalytic abilities; for example *Lactobacillus spp*. is responsible for the breakdown of ferulic acid, a phenolic acid present both in strawberry and honey, into 4-vinylguaiacol and hydroferulic acid (Pasinetti et al., 2018).

Other factors

Another aspect that must be taken into account when analyzing the bioavailability of phenolic compounds is the large inter-individual variation in the absorption, distribution, metabolism and excretion of these compounds. Some individuals may have particular polymorphisms of intestinal enzymes or xenobiotic transporters that favorably or negatively condition the bioavailability of these compounds. Differences in eating habits and the different permeability of the biological membranes (between healthy subjects and those with compromised health conditions) may also contribute to the difference in metabolic absorption and/or efficiency (Zhao et al., 2019b).

Strawberry and honey in oxidative stress

Several beneficial effects of strawberry and honey against oxidative stress-related diseases have been attributed to their high levels of nutrients, such as vitamins A, C and E, as well as to the high content of polyphenols, especially flavonoids and phenolic acids; indeed, the antioxidant capacity of these food matrices has been recognized as a marker of their bioactive compounds and, therefore, of their healthiness (Afrin et al., 2016; Cianciosi et al., 2018).

Strawberry and oxidative stress

In the last years, a large number of studies, using different *in vitro* and *in vivo* experimental models, have evaluated the antioxidant properties of strawberries (Table 1). For example, in human dermal fibroblasts (HDF), stressed with different oxidant agents, such as H_2O_2, 2,2'-Azobis(2-amidinopropane) dihydrochloride (AAPH), or UV radiation, strawberry treatment prevented and reduced the oxidative damage, by increasing cell viability, reducing ROS concentration, lipid peroxidation and DNA damage, improving mitochondrial functionality and stimulating antioxidant

enzymes through Nrf2 pathway activation (Fig. 3) (Giampieri et al., 2012; Giampieri et al., 2014a, 2014b; Gasparrini et al., 2017a). Same favorable effects were found in gastric and hepatic cells (Ávila et al., 2017; Forbes-Hernández et al., 2017; Ariza et al., 2018), in myometrial cells (Giampieri et al., 2019), in BV-2 microglia cells (Ma et al., 2018) and in adipocytes (Forbes et al., 2018), where strawberry extracts exerted cytoprotective effects, by decreasing oxidative stress and preventing cell death, thanks to high concentrations of their bioactive compounds.

To the best of our knowledge, only two studies have evaluated the antioxidant effects of strawberry after an *in vitro* digestion process, with opposite results. On one side, digested strawberry and achenes extracts were able to reduce the oxidative damage induced by AAPH in HepG2, decreasing the intracellular ROS accumulation and apoptosis rate, in a greater extent with respect to raw strawberry extract, suggesting that the bioactivity of strawberry polyphenols is maintained during the digestion process (Ariza et al., 2018). On the other side, a decrease in the antioxidant properties and bioactivity was highlighted after an *in vitro* digestion process of white strawberry in human epithelial gastric cells AGS treated with H_2O_2, suggesting that further studies are needed to completely comprehend the stability and activity of strawberry digested polyphenols (Thomas-Valdes et al., 2018).

The results obtained *in vitro* have been confirmed in studies performed in *in vivo* models, that demonstrated the effects of strawberry against oxidative stress, both in physiological and pathological conditions (Table 1). For example, in rats, strawberry consumption has shown to reduce doxorubicin-, cadmium chloride- or tetrachloride-induced oxidative damage in plasma, liver, kidney and brain, by decreasing ROS production and oxidative biomarkers levels, restoring the antioxidant enzyme activities, ameliorating the mitochondrial antioxidant status and functionality, alleviating histopathological damage, restoring hemoglobin levels, red blood and bone marrow cell counts and reducing apoptosis (Diamanti et al., 2014; Giampieri 2016; Hamed 2016; Elkhadragy and Abdel Moneim 2017; Elkhadragy et al., 2018a, 2018b). At the same time, in rats stressed with ethanol, strawberry consumption was effective in protecting gastric mucosa from

ulcerations and erosions by decreasing ROS, enhancing antioxidant defense system and reducing lipid peroxidation (Alvarez-Suarez et al., 2011). Similar results were found also in rats exposed to ^{56}Fe particles (Poulose et al., 2014), in obese rats fed a high-fat (Sandoval-Salazar et al., 2019) or a high-fructose (Fotschki al., 2018) diet and in mice stressed with acrylamide (Zhao et al., 2015). In addition, strawberry intake was effective also in slow-downing the progression of aging in old rats, by decreasing oxidative stress and ROS production, enhancing antioxidant defense and stimulating mitochondrial biogenesis and functionality through the activation of the AMP-activated protein kinase (AMPK) and Nfr2 signaling pathways (Fig. 3) (Giampieri et al., 2017b).

Many human studies have been performed in different groups of population, such as healthy subjects, obese subjects and subjects affected by metabolic syndrome or type 2 diabetes. In most of cases, strawberry consumption significantly enhanced total antioxidant capacity and vitamin C concentration in plasma (Tulipani et al., 2009; Romandini et al., 2013; Prymont-Przyminska et al., 2014; Alvarez-Suarez et al., 2014), increased erythrocytes resistance to hemolysis, augmented the metabolic activity in mononuclear cells (Tulipani et al., 2011; Tulipani et al., 2014), decreased lipid peroxidation and ox-LDL (Henning et al., 2010; Tulipani et al., 2011; Cassidy et al., 2013; Moazen et al., 2013), thus improving antioxidant status and decreasing risk factors for atherosclerosis, type 2 diabetes mellitus and metabolic syndrome.

Honey and oxidative stress

The effects of honey against oxidative stress have been evaluated in several studies (Table 2). For example, in human dermal fibroblasts stressed with different oxidant agents, such as AAPH or γ-irradiation, Manuka honey was able to decrease intracellular ROS levels, protein and lipid oxidative damage and apoptosis rate, to ameliorate mitochondrial functionality and antioxidant enzyme activities and to promote the wound healing by activating the AMPK-Nrf2 pathway (Fig. 3) (Ahmad et al., 2013; Alvarez-Suarez et al., 2016). Very similar results were found in HepG2 cells, where bee, rosemary, heather and heterofloral honeys improved the antioxidant defense system and

protected against dietary mutagen-induced DNA damage (Hassan et al., 2012; Haza and Morales, 2013), in rat bone cells with hydrocortisone-induced osteoporosis, where bee honey, in combination with Greek *Thymus vulgaris* extract, ameliorated the activity of antioxidant enzymes and decreased the levels of intracellular ROS, NO and lipid peroxidation (Abu-Serie and Habashy, 2018) and in blood cells, where different types of honeys prevented the oxidative DNA damage, the peroxidation of lipid membrane, the reduction of intracellular glutathione (GSH) and superoxide dismutase (SOD) and thus cell hemolysis (Alvarez-Suarez et al, 2012; García-Tenesaca et al., 2017; Živković et al., 2018).

The antioxidant activity of honey has been confirmed in different *in vivo* models, such as rats, mice, and humans. In rats and in mice treated with carbon tetrachloride, honey supplementation was able to prevent oxidative damage in liver and kidney, by decreasing free radical levels, lipid peroxidation, DNA oxidative damage and increasing antioxidant enzyme activities (El Denshary et al., 2012; Al-Yahya et al., 2013; Cheng et al., 2015; El-Haskoury et al., 2018). Additionally, in rats with ethanol- or with acetic acid-induced gastric ulcers, Manuka honey promoted gastroprotective effects by keeping antioxidants and inflammatory cytokines in a reduced form, inhibiting lipid peroxidation and preserving mucous glycoproteins levels (Almasaudi et al., 2016, 2017); same results were found in mice with acute alcohol-induced liver damage, where *A. cerana* honey increased antioxidant capacity and decreased lipoprotein oxidation in serum, as well as reduced peroxidation and ameliorated antioxidant defense in liver (Zhao et al., 2017). In streptozotocin-induced diabetic rats, Tualang honey, in combination with metformin or glibenclamide, significantly reduced oxidative stress, by up-regulating catalase, glutathione peroxidase and reductase activities, GSH, reduced glutathione/oxidized glutathione ratio and decreasing lipid peroxidation in pancreas and kidney tissues (Erejuwa et al., 2010, 2011), while in rats affected by dyslipidemia or colitis, honey supplementation protected colon and liver from tissue damage through the increase in SOD activities and glucose tolerance and through the reduction in total cholesterol and aspartate transaminase levels (Nooh and Nour-Eldien, 2016; Bezerra et al., 2018).

Similar trends were found in rats treated with sodium arsenite (Aliyu et al., 2013), diethyl nitrosamine (Naima et al., 2016), isoproterenol (Afroz et al., 2016) and cisplatin (Waykar and Alqadhi, 2019), where induced-oxidative stress was efficiently counteracted by honey consumption through the increase in GSH, SOD, catalase, glutathione transferase (GST), glutathione peroxidase (GPx) activities and a concomitant decrease in lipid peroxidation in liver, heart and kidney samples. Honey consumption is effective also in combating the oxidative stress induced by different kind of contaminants or additives. For example, in rats and mice exposed to aflatoxin (Yaman et al., 2016), ochratoxin A (Oršolić et al., 2017), trichlorfon (Eraslan et al., 2010), chlorpyrifos (Tanvir et al., 2015), tartrazine (El Rabey et al., 2019), honey supplementation was able to reduce lipid peroxidation, DNA damage and to increase enzymatic and non-enzymatic antioxidants in liver and kidney samples. Similar results were found in brain tissues of rats exposed to different neurotoxic agents, such as lead acetate (Abdulmajeed et al., 2016), kainic acid (Mohd Sairazi et al., 2017) and paraquat (Tang et al., 2017), in which honey supplementation, by counteracting oxidative stress, improved cognitive deficit, reduced neurodegeneration and ameliorated the toxic-induced effects.

Studies performed in humans are very few (Table 2). In female athletes and in chronic smokers, Tualang honey consumption was effective in promoting an increase in postprandial antioxidant activity and in reducing oxidative stress after 1-2 hours of consumption (Wan et al., 2015; Ahmad et al., 2017), while in male road cyclists honey supplementation decreased oxidative stress and lymphocyte DNA damage and increased antioxidant defense after moderate-to-intensive exercise training (Hajizadeh Maleki et al., 2016).

Strawberry and honey in inflammation

As mentioned, the causes of inflammation can be different, including endotoxins, viruses, variation in fatty acid levels, growth factors, imbalance in the oxidative state, but also oncogenic processes, excess body fat and a poor diet (Giampieri et al., 2017a). For this reason, a balanced diet, rich in fruits and vegetables, plays a fundamental role in the regulation of inflammatory processes that are

506 the basis of many serious diseases (Tungmunnithum et al., 2018); honey and strawberries, thanks to
507 their high content of bioactive compounds, possess remarkable inhibitory activity against
508 inflammation, as demonstrated in several both *in vitro* and *in vivo* models (Tables 3, 4).
509 *Strawberry and inflammation*
510 In recent years, the anti-inflammatory effect of strawberries has been investigated in relation to
511 different pathologies in which inflammation is the basis or the consequence. For example, in murine
512 macrophages stressed with lipopolysaccharide (LPS), the treatment with strawberry extracts lead to
513 a decrease in proinflammatory cytokines (i.e. IL-1β and IL-6) and an increase in anti-inflammatory
514 ones, such as IL-10, by downregulating the NF-κB signalling pathway, reducing inducible NOS
515 (iNOS), TNF-α and phospho-inhibitory subunit of NF-kBα (pIkBα) levels and the production of
516 NO, through the activation of the Nrf2-AMPK pathway (Fig. 3) (Liu and Lin, 2012; Gasparrini
517 et.al., 2017b, 2018a). Also a prolonged exposure to ultraviolet A (UVA)-radiation can cause an
518 inflammatory status in HDF: the pre-treatment with a cosmetic formulation based on strawberry
519 extract and Coenzyme Q_{10} was able to protect cells against damage by decreasing inflammatory
520 markers (pIkBα, NF-κB, TNF-α, IL-1β and IL-6) (Gasparrini et.al., 2017a).
521 Beside skin, the anti-inflammatory effect of strawberries has also been proven in different
522 experimental models (Table 3): for example, in human adenocarcinoma cells infected with
523 *Helicobacter Pylori* (Fumagalli et al., 2016) and in platelets isolated from volunteers and subjected
524 to an *in vitro* aggregation process (Alarcón et al., 2015), strawberry extract was able to
525 downregulate the NF-κB signalling pathway and to decrease the secretion of IL-8 and the levels of
526 TNF-α, IL-1β, CD40L and RANTES, thus modulating the mediators of acute and chronic
527 inflammation essential for cancer and cardiovascular disease onset.
528 The anti-inflammatory potential of strawberries has been confirmed also in animal models and in
529 clinical studies, involving patients affected by diseases closely correlated with inflammation. One of
530 this pathology is obesity, a global problem that has serious consequences such as the development
531 of various diseases affecting the cardiovascular system and diabetes. In this context, in a mouse

532 model of high fat diet-induced obesity, freeze-dried strawberry powder supplementation promoted
533 the reduction of several inflammation-related markers, such as C-reactive protein (CRP), TNF-α
534 and IL-6, as well as maintained normal blood glucose levels (Parelman et al., 2012). In addition,
535 strawberry consumption, in combination with blueberry, was able to reduce, in obese and diabetic
536 Wistar rats, the plasma levels of monocyte chemoattractant protein-1 (MCP-1), which is an
537 important factor in the recruitment of macrophages during the inflammatory response and to
538 decrease insulin resistance (Aranaz et al., 2017). At the same time, in mice with colitis or with
539 colon carcinogenesis, strawberry supplementation was effective in decreasing the number of pro-
540 inflammatory immune cells as well as the level of TNF-α, IL-1β, IL-17, and in downregulating the
541 NF-κB pathway, lowering the expression levels of COX-2, iNOS, and c-JUN (Shi et al., 2015; Han
542 et al., 2019).
543 Finally, in rats exposed to 1.5 Gy irradiation of ^{56}Fe, strawberries consumption was also able to
544 improve the neuronal inflammation by decreasing the levels of COX-2 and NF-κB (Shukitt-Hale et
545 al., 2013), while in mice with carrageenan-induced pleuritis, raw strawberry extract reduced the
546 leukocytic infiltrate and the levels of TNF-α, IL-6, NO and myeloperoxidase (MPO), compared to
547 the control (Duarte et al. 2018).
548 Even in humans, the intake of strawberries can exert favorable effects against inflammation: in
549 obese subjects the supplementation of strawberries lead to an improvement in the lipid profile and
550 inflammatory markers such as IL-1β, IL-6, IL-8, TNF-α and CRP (Ellis et al., 2011; Zunino et al.,
551 2012). A decrease in the levels of C-reactive protein as well as of malondialdehyde (MDA) was
552 also observed in patients with type two diabetes, supplemented with a beverage containing freeze-
553 dried strawberry for 6 weeks (Moazen et al., 2013). Finally, the consumption of freeze-dried
554 strawberry for 12 weeks was able to improve the inflammatory condition in patients affected by
555 osteoarthritis, decreasing the serum levels of TNF-α, IL- 6, IL-1β and matrix metalloproteinase
556 (MMP)-3 (Schell et al., 2017; Basu et al., 2018).
557

Honey and inflammation

In the last few years, the evaluation of anti-inflammatory activities of honey has been performed in several *in vitro* and *in vivo* models (Table 4). For example, in macrophages treated with LPS, Manuka and Gelam honeys were able to decrease the main inflammatory markers, such as iNOS, TNF-α, IL-1β, IL-6 and p-38, by inhibiting the TLR4/NF-κB pathway and concomitantly stimulating that of AMPK (Fig. 3) (Yoshizaki et al., 2010; Kassim et al., 2012a; Afrin et al., 2018b; Gasparrini et al., 2018b). At the same time, in keratinocytes treated with TNFα or with UVB rays, Fir and Tualang honeys reduced the expression of metalloprotease, pro-inflammatory cytokines (IL-1β, IL-6 and TNFα) and mediators (COX-2 and prostaglandin E2 (PGE2)), by inhibiting NF-κB translocation and IκBα degradation (Fig. 3), confirming the efficiency of honey in wound healing treatment (Ahmad et al., 2012; Majtan et al., 2013).

Together with oxidative stress, inflammation is the basis of several common chronic-degenerative diseases, as cancer and metabolic diseases. In HT-29 cells, Nenas and Gelam honeys treatment was able to downregulate the expression of NF-κB and up-regulate that of IκBα, exerting similar effects of common anti-inflammatory drugs (Wen et al., 2012; Tahir et al., 2015), while in AGS cells of gastric human carcinoma, infected with *H. pylori*, and in hamster pancreatic cells Manuka and Gelam honeys improved the chronic inflammatory state, by decreasing the expression TNF-α, IL-1β, IL-8, p-JNK and IκB Kinase β and increasing those of p-Akt (Keenan et al., 2012; Zafi et al., 2016).

Many studies performed in *in vivo* models have confirmed the anti-inflammatory effects of honey (Table 4). For example, in rats and rabbits stressed with LPS, Gelam and stingless bee honeys were able to reduce the levels of cytokines, HMGB1, NF-κB p65 and MAPK p38, to increase those of Nrf2 and to decrease the infiltration of neutrophils and the activity of MPO (Kassim et al., 2012b, 2012c; Ranneh et al., 2019). Additionally, in mice with ear or paw edema, induced by different chemical substances, such as 2-O-tetradecanoylphorbol 13-acetate (TPA), arachidonic acid, carrageenan and LPS, and formalin, the extracts of Mimosa marginata, Manuka and Kanuka honeys

were able to decrease inflammation (TNF-α, IL-6, PGE2, COX-2, NOS), neutrophil infiltration, intensity of edema and pain, by inhibiting the nuclear translocation and activation of NF-κB and the cytosolic degradation of IkBα (Fig. 3) (Kassim et al., 2010; Hussein et al., 2012, 2013; Leong et al., 2012; Borsato et al., 2014; Owoyele et al., 2014).

The wound healing activity of honey has been confirmed also in rats with intraoral wounds, with ulcers caused by a second-degree burn, or with corneal abrasion, where the topical application of honey, alone or in combination with aloe vera, and milk ointment, was effective in decreasing the levels of neutrophils and leukocytes and reducing the gene expression of tumor growth factor (TGF)-β, IL-12, TNF-α, IFN-γ and various cytokines (Uwaydat et al., 2011; Farzadinia et al., 2016; Chamani et al., 2017). Similar results were found in guinea pigs with conjunctivitis induced by *Pseudomonas aeruginosa* or *Staphylococcus aureus*, where stingless bee honey decreased the typical signs of inflammation as well as the duration of the infection and the resolution times, with the same effects of gentamicin (Ilechie et al., 2012). Finally, also in rats with induced cecal abrasion, honey administration was able to decrease the inflammatory parameters, preventing the formation of post-surgical abdominal adhesions (Giusto et al., 2017).

As for wounds, honey has been used since ancient times for airway disorders, for cough and asthma treatment. For example, in mice and rabbits with asthma induced by conalbumin or ovalbumin, honey (aerosolized, injected or ingested) was able to decrease the inflammatory response, reducing the infiltration of the eosinophils in the airways and the inflammation status in the lungs (Kamaruzaman et al.2014; El-Aidy et al., 2015; Shamshuddin and Mohd Zohdi, 2016).

In addition, honey supplementation can also be a valid ally in ameliorating inflammation in gastrointestinal and kidney diseases. In this sense, the oral intake of honey has shown to reduce the levels of the main inflammatory markers and cell infiltration, by decreasing the expression of NF-κB and inhibiting the activation of NLRP3 inflammasome and the overexpression of TXNIP in diabetic rats (Aziz et al., 2017), in rats affected by non-alcoholic steatosis (Xiao et al., 2016), in rats

609 with dextran sodium sulphate-induced ulcerative colitis (Nooh and Nour-Eldien, 2016) and in rats
610 with nephropathy induced by cisplatin treatment (Hamad et al., 2015).
611 Even clinical studies have shown a high anti-inflammatory activity of honey. For example, nasal
612 spray based on Manuka or thyme honey was effective in reducing the expression of inflammatory
613 markers (IL-6, IL-8, IL-13 MCP-1 and macrophage inflammatory proteins (MIP)-1β) in sinonasal
614 tissue as well as in decreasing the synechiae formation and epistaxis in patients suffering from
615 chronic rhinosinusitis (Hashemian et al., 2015; Manji et al., 2018). An improvement in
616 inflammatory parameters has also been observed in patients with vulvovaginal candidiasis
617 (Banaeian et al., 2017), in individuals presenting wounds or burns (Maghsoudi et al., 2011;
618 Knipping et al., 2012), in subjects with alveolar osteitis (Soni et al., 2016) and in patients with
619 inflammatory-infectious processes of open mastoid cavities (Henatsch et al., 2015). Finally, a
620 honey-based drink has also shown to be effective in reducing the inflammatory state produced in a
621 competitive sport activity, by decreasing the levels of IL-6 and IL-10 after the sporting activity of
622 soccer players (Abbey and Rankin, 2009).
623
624 **Conclusion**
625 Inflammatory and oxidative stress pathways are closely interrelated: one of them may appear before
626 or after the other, but when one of them appears the other one is most likely to appear, taking part
627 together in the pathogenesis of many chronic diseases (Chen et al., 2019). Nowadays we know that
628 a balanced and correct diet, based on food enriched in antioxidants and bioactive compounds, may
629 help in maintaining a healthy well-being and in preventing the most common human diseases, by
630 counteracting oxidative stress and inflammation. In this work we reported several studies showing
631 the antioxidant and anti-inflammatory properties of strawberry and honey from different origins in
632 several *in vitro* and *in vivo* experimental models: the possible mechanisms by which they exerts
633 these capacities seem to reside in the high content of bioactive compounds, such as vitamins and
634 phenols, which are able to scavenge free radical species, chelate metal elements, induce cellular

enzymatic and non-enzymatic antioxidant systems, decrease the production of pro-inflammatory cytokines, prostaglandins and C-reactive protein, as well as increase those of anti-inflammatory cytokines. However, it should be taken into account that the bioavailability of the bioactive compounds of these food matrices is very low. Indeed, the absorption and metabolism are very complex processes that involve: (i) the release of polyphenols from the food matrix, (ii) the solubility in the GI tract environments, (iii) the degradation during gastric and intestinal digestion, (iv) the cellular uptake by enterocytes, (v) the modifications mediated by phase I/II enzymes, (vi) the final transport into the bloodstream and succeeding tissue redistribution.

Future researches should be performed in order to (i) evaluate the fine molecular targets involved in the effect exerted by strawberry and honey, (ii) determine the effects on *in vivo* studies, (iii) examine the efficiency on prospective human studies, and (vi) develop new methods for improving the solubility, stability and permeability rate of dietary polyphenols for a possible use of these techniques in nutraceutical and pharmaceutical applications.

Acknowledgements

Tamara Forbes Hernández is supported by a "Juan de la Cierva" post-doctoral contract. DZ thanks for financial support by post-doctoral fund of Jiangsu Province, China (No. 2019K016).

Conflict of interest

The authors declare no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

Abbey, E.L., Rankin, J.W., 2009. Effect of ingesting a honey-sweetened beverage on soccer performance and exercise-induced cytokine response. Int. J. Sport Nutr. Exerc. Metab. 19, 659-672.

Abdulmajeed, W.I., Sulieman, H.B., Zubayr, M.O., Imam, A., Amin, A., Biliaminu, S.A., Oyewole, L.A., Owoyele, B.V., 2016. Honey prevents neurobehavioural deficit and oxidative stress induced by lead acetate exposure in male Wistar rats- a preliminary study. Metab. Brain Dis. 31, 37-44.

Abu-Serie M.M. and Habashy, N.H., 2018. The ameliorating effect of the combined extract from Greek Thymus vulgaris and bee's honey on the hydrocortisone-induced osteoporosis in rat bone cells via modulating the bone turnover, oxidative stress, and inflammation. RSC Adv. 8, 28341-28355.

Afrin, S., Gasparrini, M., Forbes-Hernandez, T.Y., Reboredo-Rodriguez, P., Mezzetti, B., Varela-López, A., Giampieri, F., Battino, M., 2016. Promising health benefits of the strawberry: A focus on clinical studies. J. Agric. Food Chem. 64, 4435-49.

Afrin, S., Giampieri, F., Gasparrini, M., Forbes-Hernández, T.Y., Cianciosi, D., Reboredo-Rodriguez, P., Zhang, J., Manna, P.P., Daglia, M., Atanasov, A.G., Battino, M., 2018a. Dietary phytochemicals in colorectal cancer prevention and treatment: A focus on the molecular mechanisms involved. Biotechnol. Adv. pii: S0734-9750(18)30195-2.

Afrin, S., Gasparrini, M., Forbes-Hernández, T.Y., Cianciosi, D., Reboredo-Rodriguez, P., Manna, P., Battino, M., Giampieri, F., 2018b. Protective effects of Manuka honey on LPS-treated RAW 264.7 macrophages. Part 1: Enhancement of cellular viability, regulation of cellular apoptosis and improvement of mitochondrial functionality. Food Chem Toxicol. 121, 203-213.

Afrin, S., Haneefa, S.M., Fernandez-Cabezudo, M.J., Giampieri, F., Al-Ramadi, B.K., Battino, M., 2019. Therapeutic and preventive properties of honey and its bioactive compounds in cancer: an evidence-based review. Nutr. Res. Rev. 1-27, doi: 10.1017/S0954422419000192.

Afroz, R., Tanvir, E.M., Karim, N., Hossain, M.S., Alam, N., Gan, S.H., Khalil, M.I., 2016. Sundarban honey confers protection against isoproterenol-induced myocardial infarction in wistar rats. Biomed. Res. Int. 2016, 6437641.

Ahmad, I., Jimenez, H., Yaacob, N.S., Yusuf, N., 2012. Tualang honey protects keratinocytes from ultraviolet radiation-induced inflammation and DNA damage. Photochem. Photobiol. 88, 1198-1204.

Ahmad, T.A.F.T., Jubri, Z., Rajab, N.F., Rahim, K.A., Yusof, Y.A.M., Makpol, S., 2013. Gelam Honey protects against gamma-irradiation damage to antioxidant enzymes in human diploid fibroblasts. Molecules, 18, 2200-2211.

Ahmad, N.S., Abdul Aziz, A., Kong, K.W., Hamid, M.S.A., Cheong, J.P.G., Hamzah, S.H., 2017. Dose-response effect of Tualang honey on postprandial antioxidant activity and oxidative stress in female athletes: a pilot study. J. Altern. Complement. Med. 23, 989-995.

Alarcón, M., Fuentes, E., Olate, N., Navarrete, S., Carrasco, G, Palomo, I., 2015. Strawberry extract presents antiplatelet activity by inhibition of inflammatory mediator of atherosclerosis (sP-selectin, sCD40L, RANTES, and IL-1β) and thrombus formation. Platelets 26, 224-229.

Aliyu, M., Ibrahim, S., Inuwa, H.M., Sallau, A.B., Abbas, O., Aimola, I.A., Habila, N., Uche, N.S., 2013. Ameliorative effects of acacia honey against sodium arsenite-induced oxidative stress in some viscera of male wistar albino rats. Biochem. Res. Int. 2013, 502438.

Almasaudi, S.B., El-Shitany, N.A., Abbas, A.T., Abdel-Dayem, U.A., Ali, S.S., Al Jaouni, S.K., Harakeh, S., 2016. Antioxidant, anti-inflammatory, and antiulcer potential of Manuka honey against gastric ulcer in rats. Oxid. Med. Cell Longev. 2016, 3643824.

Almasaudi, S.B., Abbas, A.T., Al-Hindi, R.R., El-Shitany, N.A., Abdel-Dayem, U.A., Ali, S.S., Saleh, R.M., Al Jaouni, S.K., Kamal, M.A., Harakeh, S.M., 2017. Manuka honey exerts antioxidant and anti-inflammatory activities that promote healing of acetic acid-induced gastric ulcer in rats. Evid. Based Complement. Alternat. Med.2017, 5413917.

726 Alvarez-Suarez, J.M., Dekanski, D., Ristic, S., Radonjić, N.V., Petronijević, N.D., Giampieri, F.,
727 Astolfi, P., González-Paramás, A.M., Santos-Buelga, C., Tulipani, S., Quiles, J.L., Mezzetti, B., and
728 Battino, M., 2011. Strawberry polyphenols attenuate ethanol-induced gastric lesion in rats by
729 activation of antioxidant enzymes and attenuation of MDA increase. PLoS ONE. 6, e25878.
730
731 Alvarez-Suarez, J.M., Giampieri, F., González-Paramás, A.M., Damiani, E., Astolfi, P., Martinez-
732 Sanchez, G., Bompadre, S., Quiles, J.L., Santos-Buelga, C., Battino, M., 2012. Phenolics from
733 monofloral honeys protect human erythrocyte membranes against oxidative damage. Food Chem.
734 Toxicol. 50, 1508–1516.
735
736 Alvarez-Suarez, J.M., Giampieri, F., Tulipani, S., Casoli, T., Di Stefano, G., González-Paramás,
737 A.M., Santos-Buelga, C., Busco, F., Quiles, J.L., Cordero, M.D., Bompadre, S., Mezzetti, B.,
738 Battino, M., 2014. One-month strawberry-rich anthocyanin supplementation ameliorates
739 cardiovascular risk, oxidative stress markers and platelet activation in humans. J. Nutr. Biochem.
740 25, 289–294.
741
742 Alvarez-Suarez, J.M., Giampieri, F., Cordero, M., Gasparrini, M., Forbes-Hernández, T., Mazzoni,
743 L., Afrin, S., Beltrán-Ayala, P., González-Paramás, A.M., Santos-Buelga, C., Varela-Lopez, A.,
744 Quiles, J.L., Battino, M., 2016. Activation of AMPK/Nrf2 signalling by Manuka honey protects
745 human dermal fibroblasts against oxidative damage by improving antioxidant response and
746 mitochondrial function promoting wound healing. J. Funct. Foods 25, 38-49.
747
748 Al-Yahya, M., Mothana, R., Al-Said, M., Al-Dosari, M., Al-Musayeib, N., Al-Sohaibani, M.,
749 Parvez, M.K., Rafatullah, S., 2013. Attenuation of CCl4-induced oxidative stress and
750 hepatonephrotoxicity by Saudi Sidr honey in rats. Evid. Based Complement. Alternat. Med. 2013,
751 569037.
752
753 Aranaz, P., Romo-Hualde, A., Zabala, M., Navarro-Herrera, D., Ruiz de Galarreta, M., Gil, A.G.,
754 Martinez, J.A., Milagro, F.I., González-Navarro, C.J., 2017. Freeze-dried strawberry and blueberry
755 attenuates diet-induced obesity and insulin resistance in rats by inhibiting adipogenesis and
756 lipogenesis. Food Funct. 8, 3999-4013.
757
758 Ariza, M.T., Forbes-Hernández, T.Y., Reboredo-Rodríguez, P., Afrin, S., Gasparrini, M.,
759 Cervantes, L., Soria, C., Martínez-Ferri, E., Battino, M., Giampieri, F., 2018. Strawberry and

achenes hydroalcoholic extracts and their digested fractions efficiently counteract the AAPH-induced oxidative damage in HepG2 cells. Int. J. Mol. Sci. 19, 2180.

Azzini, E., Vitaglione, P., Intorre, F., Napolitano, A., Durazzo, A., Foddai, M.S., Fumagalli, A., Catasta, G., Rossi, L., Venneria, E, 2010. Bioavailability of strawberryantioxidants in human subjects Br. J. Nutr. 104, 1165-1173.

Ávila, F., Theoduloz, C., López-Alarcón, C., Dorta, E., Schmeda-Hirschmann, G., 2017. Cytoprotective mechanisms mediated by polyphenols from Chilean native berries against free radical-induced damage on AGS Cells. Oxid. Med. Cell. Longev. 2017, 9808520.

Aziz, M.S.A, Giribabu, N., Rao, P.V., Salleh, N., 2017. Pancreatoprotective effects of Geniotrigona thoracica stingless bee honey in streptozotocin-nicotinamide-induced male diabetic rats. Biomed. Pharmacother. 89, 135-145.

Banaeian, S., Sereshti, M., Rafieian, M., Farahbod, F., Kheiri, S., 2017. Comparison of vaginal ointment of honey and clotrimazole for treatment of vulvovaginal candidiasis: A random clinical trial. J. Mycol. Med. 27, 494-500.

Basu, A., Kurien, B.T., Tran, H., Byrd, B., Maher, J., Schell, J., Masek, E., Barrett, J.R., Lyons, T.J., Betts, N.M., Hal Scofield, R., 2018. Strawberries decrease circulating levels of tumor necrosis factor and lipid peroxides in obese adults with knee osteoarthritis. Food Funct. 9, 6218-6226.

Bezerra, M.L.R., de Souza, E.L., de Sousa, J.M.B., Lima, M.D.S., Alves, A.F., Almeida, M.D.G., Coutinho Alves, R., Veríssimo de Araújo, E., Soares, N.L., da Silva, G.A., Magnani, M., Aquino, J.S., 2018. Effects of honey from Mimosa quadrivalvis L. (malícia) produced by the Melipona subnitida D. (jandaíra) stingless bee on dyslipidaemic rats. Food Funct. 9, 4480-4492.

Borsato, D.M., Prudente, A.S., Döll-Boscardin, P.M., Borsato, A.V., Luz, C.F., Maia, B.H., Cabrini, D.A., Otuki, M.F., Miguel, M.D., Farago, P.V., Miguel, O.G., 2014. Topical anti-inflammatory activity of a monofloral honey of Mimosa scabrella provided by Melipona marginata during winter in southern Brazil. J. Med. Food. 17, 817-825.

Brglez Mojzer, E., Knez Hrnčič, M., Škerget, M., Knez, Ž., Bren, U., 2016. Polyphenols: extraction methods, antioxidative action, bioavailability and anticarcinogenic effects. Molecules. 21, 901.

Cao, H., Ou, J.Y., Chen, L., Zhang, Y.B., Szkudelski, T., Delmas, D., Daglia, M., Xiao J.B., 2019. Dietary polyphenols for managing type 2 diabetes: Human studies and clinical trials. Crit. Rev. Food Sci. Nutr., 59, 3371-3379.

Carkeet, C., Clevidence, B.A., Novotny, J.A., 2008. Anthocyanin excretion by humans increases linearly with increasing strawberry dose J. Nutr. 138, 897–902.

Cassidy, A., Mukamal, K.J., Liu, L., Franz, M., Eliassen, A.H., Rimm, E.B, 2013. A high anthocyanin intake is associated with a reduced risk of myocardial infarction in young and middle-aged women. Circulation. 127, 188–196.

Cerdá, B., Tomás-Barberán, F.A., Espín, J.C., 2005. Metabolism of antioxidant and chemopreventive ellagitannins from strawberries, raspberries, walnuts, and oak-aged wine in humans: identification of biomarkers and individual variability J. Agric. Food Chem. 53, 227-235.

Cezar, T. L., Martinez, R. M., da Rocha, C., Melo, C. P., Vale, D. L., Borghi, S. M., Fattori, V., Vignoli, J. A., Camilios-Neto, D., Baracat, M. M., Sandra R. Georgetti, S. R., Verri, W. A., Casagrande, R., 2019. Treatment with maresin 1, a docosahexaenoic acid-derived pro-resolution lipid, protects skin from inflammation and oxidative stress caused by UVB irradiation. Sci. Rep. 91, 3062.

Chamani, G., Zarei, M.R., Mehrabani, M., Mehdavinezhad, A., Vahabian, M., Ahmadi-Motamayel, F., 2017. Evaluation of Honey as a Topical Therapy for Intraoral Wound Healing in Rats. Wounds 29, 80-86.

Chen, L., Teng, H., Jia, Z., Battino, M., Miron, A., Yu, Z., Cao, H., Xiao, J., 2018a. Intracellular signaling pathways of inflammation modulated by dietary flavonoids: The most recent evidence. Crit. Rev. Food. Sci. Nutr. 58, 2908-2924.

824 Chen, L., Teng, H., Xie, Z.L., Cao, H., Cheang, W.S., Skalicka-Woniak, K., Georgiev, M.I., Xiao
825 J.B., 2018b. Modifications of dietary flavonoids towards improved bioactivity: An update on
826 structure-activity relationship. Crit. Rev. Food Sci. Nutr. 58, 513-527.
827 Chen, T., Luo, W., Wu, G., Wu, L., Huang, S., Li, J., Wang, J., Hu, X., Huang, W., Liang, G,. 2019.
828 A novel MyD88 inhibitor LM9 prevents atherosclerosis by regulating inflammatory responses and
829 oxidative stress in macrophages. Toxicol. Appl. Pharmacol. 370, 44-55.
830
831 Cheng, N., Wu, L., Zheng, J., Cao, W., 2015. Buckwheat honey attenuates carbon tetrachloride-
832 induced liver and DNA damage in mice. Evid. Based Complement. Alternat. Med. 2015, 987385.
833
834 Choi, S. H., Sviridov, D., Miller, Y. I., 2017. Oxidized cholesteryl esters and inflammation.
835 Biochim. Biophys. Acta. 1862, 393-397.
836
837 Cianciosi, D., Forbes-Hernández, T.Y., Afrin, S., Gasparrini, M., Reboredo-Rodriguez, P., Manna,
838 P.P., Zhang, J., Bravo Lamas, L., Martínez Flórez, S., Agudo Toyos, P., Quiles, J.L., Giampieri, F.,
839 Battino, M., 2018. Phenolic Compounds in Honey and Their Associated Health Benefits: A
840 Review. Molecules. 23, 2322.
841
842 Diamanti, J., Mezzetti, B., Giampieri, F., Alvarez-Suarez, J.M., Quiles, J.L., Gonzalez-Alonso, A.,
843 Ramirez-Tortosa, M.C., Granados-Principal, S., Gonzáles-Paramás, A.M,, Santos-Buelga, C.,
844 Battino, M., 2014. Doxorubicin-induced oxidative stress in rats is efficiently counteracted by
845 dietary anthocyanin differently enriched strawberry (Fragaria × ananassa Duch.). J. Agric. Food
846 Chem. 62, 3935-3943.
847
848 Duan, J., Zhang, Q., Hu, X., Lu, D., Yu, W., Bai, H., 2019. N4-acetylcytidine is required for
849 sustained NLRP3 inflammasome activation via HMGB1 pathway in microglia. Cell. Signal. 58, 44-
850 52.
851
852 Duarte, L.J., Chaves, V.C., Nascimento, M.V.P.D.S., Calvete, E., Li, M., Ciraolo, E., Ghigo, A.,
853 Hirsch, E., Simões, C.M.O., Reginatto, F.H., Dalmarco, E.M., 2018. Molecular mechanism of
854 action of Pelargonidin-3-O-glucoside, the main anthocyanin responsible for the anti-inflammatory
855 effect of strawberry fruits. Food Chem. 247, 56-65.
856

857 Dunn, J. D., Alvarez, L. A., Zhang, X., Soldati, T., 2015. Reactive oxygen species and
858 mitochondria: a nexus of cellular homeostasis. Redox. Biol. 6, 472-485.
859
860 El Denshary, E.S., Al-Gahazali, M.A., Mannaa, F.A., Salem, H.A., Hassan, N.S., Abdel-Wahhab,
861 M.A., 2012. Dietary honey and ginseng protect against carbon tetrachloride-induced
862 hepatonephrotoxicity in rats. Exp. Toxicol. Pathol. 64, 753-760.
863
864 El Rabey, H.A., Al-Seeni, M.N., Al-Sieni, A.I., Al-Hamed, A.M., Zamzami, M.A., Almutairi, F.M.
865 2019. Honey attenuates the toxic effects of the low dose of tartrazine in male rats. J. Food Biochem.
866 43, e12780.
867
868 El-Aidy, W.K., Ebeid, A.A., Sallam Ael, R., Muhammad, I.E., Abbas, A.T., Kamal, M.A., Sohrab,
869 S.S., 2015. Evaluation of propolis, honey, and royal jelly in amelioration of peripheral blood
870 leukocytes and lung inflammation in mouse conalbumin-induced asthma model. Saudi J. Biol. Sci.
871 22, 780-788.
872
873 El-Haskoury, R., Al-Waili, N., Kamoun, Z., Makni, M., Al-Waili, H., Lyoussi B., 2018.
874 Antioxidant activity and protective effect of carob honey in CCl4-induced kidney and liver injury.
875 Arch. Med. Res.49, 306-313.
876
877 Elkhadragy, M.F., Abdel Moneim, A.E., 2017. Protective effect of Fragaria ananassa methanolic
878 extract on cadmium chloride ($CdCl_2$)-induced hepatotoxicity in rats. Toxicol. Mech. Methods. 27,
879 335-345.
880
881 Elkhadragy, M.F., Al-Olayan, E.M., Al-Amiery, A.A., Abdel Moneim, A.E., 2018a. Protective
882 effects of Fragaria ananassa extract against cadmium chloride-induced acute renal toxicity in rats.
883 Biol. Trace Elem. Res. 181, 378-387.
884
885 Elkhadragy, M.F., Kassab, R.B., Metwally, D., Almeer, R.S., Abdel-Gaber, R., Al-Olayan, E.M.,
886 Essawy, E.A., Amin, H.K., Abdel Moneim, A.E., 2018b. Protective effects of Fragaria ananassa
887 methanolic extract in a rat model of cadmium chloride-induced neurotoxicity. Biosci. Rep. 38,
888 BSR20180861.
889

Ellis, C.L., Edirisinghe, I., Kappagoda, T., Burton-Freeman, B., 2011. Attenuation of meal-induced inflammatory and thrombotic responses in overweight men and women after 6-week daily strawberry (Fragaria) intake. A randomized placebo-controlled trial. J. Atheroscler. Thromb. 18, 318-327.

Eraslan, G., Kanbur, M., Silici, S., Karabacak, M., 2010. Beneficial effect of pine honey on trichlorfon induced some biochemical alterations in mice. Ecotoxicol. Environ. Saf. 73,1084-1091.

Erejuwa, O.O., Sulaiman, S.A., Wahab, M.S., Salam, S.K., Salleh, M.S., Gurtu, S., 2010. Antioxidant protective effect of glibenclamide and metformin in combination with honey in pancreas of streptozotocin-induced diabetic rats. Int. J. Mol. Sci. 11, 2056-2066.

Erejuwa, O.O., Sulaiman, S.A., Wahab, M.S., Salam, S.K., Salleh, M.S., Gurtu, S., 2011. Comparison of antioxidant effects of honey, glibenclamide, metformin, and their combinations in the kidneys of streptozotocin-induced diabetic rats. Int. J. Mol. Sci. 12, 829-843.

Farzadinia, P., Jofreh, N., Khatamsaz, S., Movahed, A., Akbarzadeh, S., Mohammadi, M., Bargahi, A., 2016. Anti-inflammatory and Wound Healing Activities of Aloe vera, Honey and Milk Ointment on Second-Degree Burns in Rats. Int. J. Low Extrem. Wounds 15, 241-247.

Felgines, C., Talavéra, S., Gonthier, M. P., Texier, O., Scalbert, A., Lamaison, J.L., Rémésy, C., 2003. Strawberry anthocyanins are recovered in urine as glucuro-and sulfoconjugates in humans J. Nutr. 133, 1296–1301.

Forbes-Hernández, T.Y., Gasparrini, M., Afrin, S., Cianciosi, D., González-Paramás, A.M., Santos-Buelga, C., Mezzetti, B., Quiles, J.L., Battino, M., Giampieri, F., Bompadre, S., 2017. Strawberry (cv. Romina) methanolic extract and anthocyanin-enriched fraction improve lipid profile and antioxidant status in HepG2 Cells. Int. J. Mol. Sci. 18, 1149.

Forbes-Hernández, T.Y., Afrin, S., Cianciosi, D., Manna, P.P., Zhang, J., Gasparrini, M., Reboredo-Rodríguez, P., 2018. Strawberry extract attenuates oxidative stress in 3T3-L1 cells. J. Berry Res. 8, 193-203.

Forstermann, U. and Li, H., 2011. Therapeutic effect of enhancing endothelial nitric oxide synthase (eNOS) expression and preventing eNOS uncoupling. Br. J. Pharmacol. 164, 213–223.

Fotschki, B., Juśkiewicz, J., Kołodziejczyk, K., Jurgoński, A., Kosmala, M., Milala, J., Ognik, K., Zduńczyk, Z., 2018. Protective effects of ellagitannin-rich strawberry extracts on biochemical and metabolic disturbances in rats fed a diet high in fructose. Nutrients. 10, 445.

Fumagalli, M., Sangiovanni, E., Vrhovsek, U., Piazza, S., Colombo, E., Gasperotti, M., Mattivi, F., De Fabiani, E., Dell'Agli, M., 2016. Strawberry tannins inhibit IL-8 secretion in a cell model of gastric inflammation. Pharmacol. Res. 111, 703-712.

García-Tenesaca, M., Navarrete, E.S., Iturralde, G.A., Villacrés Granda, I.M., Tejera, E., Beltrán-Ayala, P., Giampieri, F., Battino, M., Alvarez-Suarez, J.M., 2017. Influence of botanical origin and chemical composition on the protective effect against oxidative damage and the capacity to reduce *in vitro* bacterial biofilms of monofloral honeys from the Andean region of Ecuador. Int. J. Mol. Sci. 19, 45.

Gasparrini, M., Forbes-Hernandez, T.Y., Afrin, S., Reboredo-Rodriguez, P., Cianciosi, D., Mezzetti, B., Quiles, J.L., Bompadre, S., Battino, M., Giampieri, F., 2017a. Strawberry-based cosmetic formulations protect human dermal fibroblasts against UVA-induced damage. Nutrients 9, 605.

Gasparrini, M., Forbes-Hernandez, T.Y., Giampieri, F., Afrin, S., Alvarez-Suarez, J.M., Mazzoni, L., Mezzetti, B., Quiles, JL., Battino, M., 2017b. Anti-inflammatory effect of strawberry extract against LPS-induced stress in RAW 264.7 macrophages. Food Chem. Toxicol. 102, 1-10.

Gasparrini, M., Giampieri, F., Forbes-Hernandez, T.Y., Afrin, S., Cianciosi, D., Reboredo-Rodriguez, P., Varela-Lopez, A., Zhang, J., Quiles, J.L., Mezzetti, B., Bompadre, S., Battino, M., 2018a. Strawberry extracts efficiently counteract inflammatory stress induced by the endotoxin lipopolysaccharide in Human Dermal Fibroblast. Food Chem. Toxicol. 114, 128-140.

Gasparrini, M., Afrin, S., Forbes-Hernández, T.Y., Cianciosi, D., Reboredo-Rodriguez, P., Amici, A., Battino, M., Giampieri, F., 2018b. Protective effects of Manuka honey on LPS-treated RAW 264.7 macrophages. Part 2: Control of oxidative stress induced damage, increase of antioxidant enzyme activities and attenuation of inflammation. Food Chem. Toxicol. 120, 578-587.

957 Giampieri, F., Alvarez-Suarez, J.M., Tulipani, S., Gonzàles-Paramàs, A.M., Santos-Buelga, C.,
958 Bompadre, S., Quiles, J.L., Mezzetti, B., Battino, M., 2012. Photoprotective potential of strawberry
959 (Fragaria × ananassa) extract against UV-A irradiation damage on human fibroblasts. J. Agric. Food
960 Chem. 60, 2322-2327.
961
962 Giampieri, F., Alvarez-Suarez, J.M., Mazzoni, L., Forbes-Hernandez, T.Y., Gasparrini, M.,
963 Gonzàlez-Paramàs A.M., Santos-Buelga, C., Quiles, J.L., Bompadre, S., Mezzetti, B., Battino, M.,
964 2014a. Polyphenol-rich strawberry extract protects human dermal fibroblasts against hydrogen
965 peroxide oxidative damage and improves mitochondrial functionality. Molecules. 19, 7798-816.
966
967 Giampieri, F., Alvarez-Suarez, J.M., Mazzoni, L., Forbes-Hernandez, T.Y., Gasparrini, M.,
968 Gonzàlez-Paramàs, A.M., Santos-Buelga, C., Quiles, J.L., Bompadre, S., Mezzetti, B., Battino, M.,
969 2014b. An anthocyanin-rich strawberry extract protects against oxidative stress damage and
970 improves mitochondrial functionality in human dermal fibroblasts exposed to an oxidizing agent.
971 Food Funct. 5, 1939-1948.
972
973 Giampieri, F., Alvarez-Suarez, J.M., Gasparrini, M., Forbes-Hernandez, T.Y., Afrin S., Bompadre,
974 S., Rubini, C., Zizzi, A., Astolfi, P., Santos-Buelga, C., González-Paramás, A.M., Quiles, J.L.,
975 Mezzetti, B., Battino, M., 2016. Strawberry consumption alleviates doxorubicin-induced toxicity by
976 suppressing oxidative stress. Food Chem. Toxicol. 94, 128-137.
977
978 Giampieri, F., Forbes-Hernandez, T.Y., Gasparrini, M., Afrin, S., Cianciosi, D., Reboredo-
979 Rodriguez, P., Varela-Lopez, A., Quiles, J.L., Mezzetti, B., Battino M., 2017a. The healthy effects
980 of strawberry bioactive compounds on molecular pathways related to chronic diseases. Ann. N. Y.
981 Acad. Sci. 398, 62-71.
982
983 Giampieri, F., Alvarez-Suarez, J.M., Cordero, M.D., Gasparrini, M., Forbes-Hernandez, T.Y.,
984 Afrin, S., Santos-Buelga, C., González-Paramás, A.M., Astolfi, P., Rubini, C., Zizzi, A., Tulipani,
985 S., Quiles, J.L., Mezzetti, B., Battino, M, 2017b. Strawberry consumption improves aging-
986 associated impairments, mitochondrial biogenesis and functionality through the AMP-activated
987 protein kinase signaling cascade. Food Chem. 234, 464-471.
988
989 Giampieri, F., Islam, M.S., Greco, S., Gasparrini, M., Forbes Hernandez, T.Y., Delli Carpini, G.,
990 Giannubilo, S.R., Ciavattini, A., Mezzetti, B., Mazzoni, L., Capocasa, F., Castellucci, M., Battino,

M., Ciarmela, P., 2019. Romina: A powerful strawberry with in vitro efficacy against uterine leiomyoma cells. J. Cell. Physiol. 234, 7622-7633.

Gill, R., Tsung, A., Billiar, T., 2010. Linking oxidative stress to inflammation: Toll-like receptors. Free Radic. Biol. Med. 48, 1121-1132.

Ginnan, R., Jourd'heuil, F. L., Guikema, B., Simons, M., Singer, H. A., Jourd'heuil, D., 2013. NADPH oxidase 4 is required for interleukin-1β-mediated activation of protein kinase Cδ and downstream activation of c-jun N-terminal kinase signaling in smooth muscle. Free Radic. Biol. Med. 54, 125-134.

Giusto, G., Vercelli, C., Iussich, S., Audisio, A., Morello, E., Odore, R., Gandini, M., 2017. A pectin-honey hydrogel prevents postoperative intraperitoneal adhesions in a rat model. BMC Vet. Res. 13:55.

Goldszmid, R.S., Trinchieri, G., 2012. The price of immunity. Nat. Immunol. 13, 932-938.

Hajizadeh Maleki, B., Tartibian, B., Mooren, F.C., Krüger, K., FitzGerald, L.Z., Chehrazi, M., 2016. A randomized controlled trial examining the effects of 16 weeks of moderate-to-intensive cycling and honey supplementation on lymphocyte oxidative DNA damage and cytokine changes in male road cyclists. Cytokine. 88, 222-231.

Hamed, S.S., Al-Yhya, N.A., El-Khadragy, M.F., Al-Olayan, E.M., Alajmi, R.A., Hassan, Z.K., Hassan, S.B., Abdel Moneim, A.E., 2016. The protective properties of the strawberry (Fragaria ananassa) against carbon tetrachloride-induced hepatotoxicity in rats mediated by anti-apoptotic and upregulation of antioxidant genes expression effects. Front. Physiol. 7, 325.

Han, Y., Song, M., Gu, M., Ren, D., Zhu, X., Cao, X., Li, F., Wang, W., Cai, X., Yuan, B., Goulette, T., Zhang, G., Xiao, H., 2019. Dietary Intake of Whole Strawberry Inhibited Colonic Inflammation in Dextran-Sulfate-Sodium-Treated Mice via Restoring Immune Homeostasis and Alleviating Gut Microbiota Dysbiosis. J. Agric. Food Chem. doi: 10.1021/acs.jafc.8b05581.

Hashemian, F., Baghbanian, N., Majd, Z., Rouini, M.R., Jahanshahi, J., Hashemian, F., 2015. The effect of thyme honey nasal spray on chronic rhinosinusitis: a double-blind randomized controlled clinical trial. Eur. Arch. Otorhinolaryngol. 272, 1429-1435.

Hassan, M.I., Mabrouk, G.M., Shehata, H.H., Aboelhussein, M.M., 2012. Antineoplastic effects of bee honey and Nigella sativa on hepatocellular carcinoma cells. Integr. Cancer Ther. 11, 354-363.

Haza, A.I., Morales, P., 2013. Spanish honeys protect against food mutagen-induced DNA damage. J. Sci. Food Agric. 93, 2995-3000.

Henatsch, D., Wesseling, F., Briedé, J.J., Stokroos, R.J., 2015. Treatment of chronically infected open mastoid cavities with medical honey: a randomized controlled trial. Otol. Neurotol. 36, 782-787.

Henning, S.M., Seeram, N.P., Zhang, Y., Li, L., Gao, K., Lee, R.P., Wang, D.C., Zerlin, A., Karp, H., Thames, G., Kotlerman, J., Li, Z., Heber, D., 2010. Strawberry consumption is associated with increased antioxidant capacity in serum. J. Med. Food. 13, 116-122.

Hollands, W., Brett, G. M., Dainty, J.R., Teucher, B., Kroon, P.A., 2008. Urinary excretion of strawberry anthocyanins is dose dependent for physiological oral doses of fresh fruit Mol. Nutr. Food Res. 52, 1097–1105.

Hu, B., Liu, X., Zhang, C., Zeng, X., 2017. Food macromolecule based nanodelivery systems for enhancing the bioavailability of polyphenols. J. Food Drug Anal. 25, 3-15.

Hussein, S.Z., Mohd Yusoff, K., Makpol, S., Mohd Yusof, Y.A., 2012. Gelam honey inhibits the production of proinflammatory, mediators NO, PGE(2), TNF-α, and IL-6 in carrageenan-induced acute paw edema in rats. Evid. Based Complement. Alternat. Med. 2012, 109636.

Hussein, S.Z., Mohd Yusoff, K., Makpol, S., Mohd Yusof, Y.A., 2013. Gelam honey attenuates carrageenan-induced rat paw inflammation via NF-κB pathway. PLoS One 8, e72365.

Ilechie, A.A., Kwapong, P.K., Mate-Kole Kyei, E., Darko-Takyi, C., 2012. The efficacy of stingless bee honey for the treatment of bacteria-induced conjunctivitis in guinea pigs. J. Exp. Pharmacol. 4, 63-68.

Jhang, J.J., Cheng, Y.T., Ho, C.Y., Yen, G.C., 2015. Monosodium urate crystals trigger Nrf2-and heme oxygenase-1-dependent inflammation in THP-1 cells. Cell. Mol. Immunol. 12, 424.

Kamaruzaman, N.A., Sulaiman, S.A., Kaur, G., Yahaya, B., 2014. Inhalation of honey reduces airway inflammation and histopathological changes in a rabbit model of ovalbumin-induced chronic asthma. BMC Complement Altern. Med. 14, 176.

Kassim, M., Achoui, M., Mansor, M., Yusoff, K.M., 2010. The inhibitory effects of Gelam honey and its extracts on nitric oxide and prostaglandin E(2) in inflammatory tissues. Fitoterapia 81, 1196-1201.

Kassim, M., Mansor, M., Suhaimi, A., Ong, G., Yusoff, K.M., 2012a. Gelam honey scavenges peroxynitrite during the immune response. Int. J. Mol. Sci. 13, 12113-12129.

Kassim, M., Yusoff, K.M., Ong, G., Sekaran, S., Yusof, M.Y., Mansor, M., 2012b. Gelam honey inhibits lipopolysaccharide-induced endotoxemia in rats through the induction of heme oxygenase-1 and the inhibition of cytokines, nitric oxide, and high-mobility group protein B1. Fitoterapia 83, 1054-1059.

Kassim, M., Mansor, M., Al-Abd, N., Yusoff, K.M., 2012c. Gelam honey has a protective effect against lipopolysaccharide (LPS)-induced organ failure. Int. J. Mol. Sci. 13, 6370-6381.

Kawabata, K., Yoshioka, Y., Terao, J., 2019. Role of intestinal microbiota in the bioavailability and physiological functions of dietary polyphenols. Molecules. 24, 370.

Keenan, J.I., Salm, N., Wallace, A.J., Hampton, M.B., 2012. Using food to reduce H. pylori-associated inflammation. Phytother. Res. 26, 1620-1625.

Khurana, N., Sikka, S., 2018. Targeting crosstalk between Nrf-2, NF-κB and androgen receptor signaling in prostate cancer. Cancers (Basel) 10, 352.

Kim, A. R., Lee, M. S., Shin, T. S., Hua, H., Jang, B. C., Choi, J. S., Byun, D. S., Utsuki, T., Ingram, D., Kim, H. R., 2011. Phlorofucofuroeckol A inhibits the LPS-stimulated iNOS and COX-2

expressions in macrophages via inhibition of NF-κB, Akt, and p38 MAPK. Toxicol. In Vitro 25, 1789-1795.

Knipping, S., Grünewald, B., Hirt, R., 2012. Medical honey in the treatment of wound-healing disorders in the head and neck area. HNO 60, 830-836.

Leong, A.G., Herst, P.M., Harper, J.L., 2012. Indigenous New Zealand honeys exhibit multiple anti-inflammatory activities. Innate Immun. 18, 459-466.

Liu, C.J., Lin, J.Y., 2012. Anti-inflammatory and anti-apoptotic effects of strawberry and mulberry fruit polysaccharides on lipopolysaccharide-stimulated macrophages through modulating pro-/anti-inflammatory cytokines secretion and Bcl-2/Bak protein ratio. Food Chem. Toxicol. 50, 3032-3039.

Liu, A.B., Tao, S., Lee, M. J., Hu, Q., Meng, X., Lin, Y., Yang, C. S., 2018. Effects of gut microbiota and time of treatment on tissue levels of green tea polyphenols in mice. Biofactors. 44, 348-360.

Luca, S.V., Macovei, I., Bujor, A., Miron, A., Skalicka-Woźniak, K., Aprotosoaie, A.C., Trifan, A., 2019. Bioactivity of dietary polyphenols: The role of metabolites. Crit. Rev. Food Sci. Nutr. 7, 1-34.

Lugrin, J., Rosenblatt-Velin, N., Parapanov, R., Liaudet, L., 2014. The role of oxidative stress during inflammatory processes. J. Biol. Chem. 395, 203-230.

Ma, H., Johnson, S.L., Liu, W., DaSilva, N.A., Meschwitz, S., Dain, J.A., Seeram, N.P., 2018. Evaluation of polyphenol anthocyanin-enriched extracts of blackberry, black raspberry, blueberry, cranberry, red raspberry, and strawberry for free radical scavenging, reactive carbonyl species trapping, anti-glycation, anti-β-amyloid aggregation, and microglial neuroprotective effects. Int. J. Mol. Sci. 19, 461.

Maghsoudi, H., Salehi, F., Khosrowshahi, M.K., Baghaei, M., Nasirzadeh, M., Shams, R., 2011. Comparison between topical honey and mafenide acetate in treatment of burn wounds. Ann. Burns Fire Disasters 24, 132-137.

Majtan, J., Bohova, J., Garcia-Villalba, R., Tomas-Barberan, F.A., Madakova, Z., Majtan, T., Majtan, V., Klaudiny, J., 2013. Fir honeydew honey flavonoids inhibit TNF-α-induced MMP-9 expression in human keratinocytes: a new action of honey in wound healing. Arch. Dermatol. Res. 305, 619-627.

Manji, J., Thamboo, A., Sunkaraneni, V., Singh, A., Tebbutt, S., Garnis, C., 2018. The association of Leptospermum honey with cytokine expression in the sinonasal epithelium of chronic rhinosinusitis patients. World J. Otorhinolaryngol. Head Neck Surg. 5, 19-25.

Marín, L., Miguélez, E. M., Villar, C. J., Lombó, F., 2015. Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. Biomed Res. Int. 2015, 905215.

Martinon, F. 2010. Signaling by ROS drives inflammasome activation. Eur. J. Immunol. 40, 616-619.

Mihai, S., Codrici, E., Popescu, I. D., Enciu, A. M., Albulescu, L., Necula, L. G., Mambet, C., Anton, G., Tanase, C., 2018. Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. J. Immunol. Res. 2018, 16.

Moazen, S., Amani, R., Homayouni Rad, A., Shahbazian, H., Ahmadi, K., Taha Jalali, M., 2013. Effects of freeze-dried strawberry supplementation on metabolic biomarkers of atherosclerosis in subjects with type 2 diabetes: a randomized double-blind controlled trial. Ann. Nutr. Metab. 63, 256-264.

Mohd Sairazi, N.S., Sirajudeen, K.N.S., Asari, M.A., Mummedy, S., Muzaimi, M., Sulaiman, S.A., 2017. Effect of Tualang honey against KA-induced oxidative stress and neurodegeneration in the cortex of rats. BMC Complement Altern. Med. 17, 31.

Mullen, W., Edwards, C.A., Serafini, M., Crozier, A., 2008. Bioavailability of pelargonidin-3-O-glucoside and its metabolites in humans following the ingestion of strawberries with and without cream J. Agric. Food Chem. 56, 713-719.

Murota, K., Nakamura, Y., Uehara, M., 2018. Flavonoid metabolism: The interaction of metabolites and gut microbiota. Biosci. Biotechnol. Biochem. 82, 600-610.

Naima, Z.M., Hanan, F.A., Hatem, A.M.E.M., Hadeer, E.E.S., 2016. Bee honey modulates the oxidant-antioxidant imbalance in diethyl nitrosamine-initiated rat hepatocellular carcinoma. J. App. Pharm. Sci. 6, 156-163.

Nooh, H.Z., Nour-Eldien, N.M., 2016. The dual anti-inflammatory and antioxidant activities of natural honey promote cell proliferation and neural regeneration in a rat model of colitis. Acta Histochem. 118, 588-595.

Olivero-David, R., Ruiz-Roso, M. B., Caporaso, N., Perez-Olleros, L., De las Heras, N., Lahera, V., Ruiz-Roso, B., 2018. In vivo bioavailability of polyphenols from grape by-product extracts, and effect on lipemia of normocholesterolemic Wistar rats. J. Sci. Food Agric. 98, 5581-5590.

Oršolić, N., Jazvinšćak Jembrek, M., Terzić, S., 2017. Honey and quercetin reduce ochratoxin A-induced DNA damage in the liver and the kidney through the modulation of intestinal microflora. Food Agric. Immunol. 28, 812-833.

Owoyele, B.V., Oladejo, R.O., Ajomale, K., Ahmed, R.O., Mustapha, A., 2014. Analgesic and anti-inflammatory effects of honey: the involvement of autonomic receptors. Metab. Brain Dis. 29, 167-173.

Parelman, M.A., Storms, D.H., Kirschke, C.P., Huang, L., Zunino, S.J., 2012. Dietary strawberry powder reduces blood glucose concentrations in obese and lean C57BL/6 mice, and selectively lowers plasma C-reactive protein in lean mice. Br. J.Nutr. 108, 1789-1799.

Parra-Ortiz, E., Browning, K. L., Damgaard, L. S., Nordström, R., Micciulla, S., Bucciarelli, S., Malmsten, M. 2019. Effects of oxidation on the physicochemical properties of polyunsaturated lipid membranes. J. Colloid. Interface Sci. 538, 404-419.

Pasinetti, G.M., Singh, R., Westfall, S., Herman, F., Faith, J., Ho, L., 2018. The role of the gut microbiota in the metabolism of polyphenols as characterized by gnotobiotic mice. J. Alzheimers Dis. 63, 409-421.

Poulose, S.M., Bielinski, D.F., Carrihill-Knoll, K.L., Rabin, B.M., Shukitt-Hale B3., 2014. Protective effects of blueberry- and strawberry diets on neuronal stress following exposure to $^{(56)}$Fe particles. Brain Res. 1593, 9-18.

Prymont-Przyminska, A., Zwolinska, A., Sarniak, A., Wlodarczyk, A., Krol, M., Nowak, M., de Graft-Johnson, J., Padula, G., Bialasiewicz, P., Markowski, J., Rutkowski, K.P., Nowak, D., 2014. Consumption of strawberries on a daily basis increases the non-urate 2,2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging activity of fasting plasma in healthy subjects. J. Clin. Biochem. Nutr. 55, 48-55.

Quan, Y., Gong, L., He, J., Zhou, Y., Liu, M., Cao, Z., Li, Y., Peng, C., 2019. Aloe emodin induces hepatotoxicity by activating NF-κB inflammatory pathway and P53 apoptosis pathway in zebrafish. Toxicol. Lett. 306, 66-79.

Ranneh, Y., Akim, A.M., Hamid, H.A., Khazaai, H., Fadel, A., Mahmoud, A.M., 2019. Stingless bee honey protects against lipopolysaccharide induced-chronic subclinical systemic inflammation and oxidative stress by modulating Nrf2, NF-κB and p38 MAPK. Nutr. Metab. (Lond) 16, 15.

Raucci, A., Di Maggio, S., Scavello, F., D'Ambrosio, A., Bianchi, M. E., Capogrossi, M. C., 2019. The Janus face of HMGB1 in heart disease: a necessary update. Cell. Mol. Life Sci. 76, 211–229.

Ray, P.D., Huang B.W., and Tsuji Y., 2012. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. Cell. Signal. 24, 981-90.

Romandini, S., Mazzoni, L., Giampieri, F., Tulipani, S., Gasparrini, M., Forbes-Hernandez, T.Y., Locorotondo, N., D'Alessandro, M., Mezzetti, B., Bompadre, S. and Alvarez-Suarez, J.M., 2013. Effects of an acute strawberry (Fragaria × ananassa) consumption on the plasma antioxidant status of healthy subjects. J. Berry Res. 3, 169–179.

Ruiz, S., Pergola, P. E., Zager, R. A., Vaziri, N. D., 2013. Targeting the transcription factor Nrf2 to ameliorate oxidative stress and inflammation in chronic kidney disease. Kidney Int. 83, 1029-1041.

Russell, W.R., Scobbie, L., Labat, A., Duthie, G.G., 2009. Selective bio-availability of phenolic acids from Scottish strawberries Mol. Nutr. Food Res. 53, S85-S91.

Safi, S.Z., Batumalaie, K., Qvist, R., Mohd Yusof, K., Ismail, I.S., 2016. Gelam Honey Attenuates the Oxidative Stress-Induced Inflammatory Pathways in Pancreatic Hamster Cells. Evid. Based Complement. Alternat. Med. 2016, 5843615.

Sandoval-Salazar, C., Oviedo-Solís, C.I., Lozoya-Gloria, E., Aguilar-Zavala, H., Solís-Ortiz, M.S., Pérez-Vázquez, V., Balcón-Pacheco, C.D., Ramírez-Emiliano, J., 2019. Strawberry intake ameliorates oxidative stress and decreases GABA levels induced by high-fat diet in frontal cortex of rats. Antioxidants (Basel). 8(3). pii: E70. doi: 10.3390/antiox8030070.

Santhakumar, A. B., Battino, M., Alvarez-Suarez, J. M., 2018. Dietary polyphenols: Structures, bioavailability and protective effects against atherosclerosis. Food Chem. Toxicol. 113, 49-65.

Schell, J., Scofield, R.H., Barrett, J.R., Kurien, B.T., Betts, N., Lyons, T.J., Zhao, Y.D., Basu, A., 2017. Strawberries Improve Pain and Inflammation in Obese Adults with Radiographic Evidence of Knee Osteoarthritis. Nutrients 9, E949.

Schramm, D.D., Karim, M., Schrader, H.R., Holt, R.R., Cardetti, M., Keen, C.L., 2003. Honey with high levels of antioxidants can provide protection to healthy human subjects. J. Agric. Food Chem. 51, 1732-1735.

Serbulea, V., Upchurch, C. M., Ahern, K. W., Bories, G., Voigt, P., DeWeese, D. E., Meher, A.K., Harris, T. E., Leitinger, N., 2018. Macrophages sensing oxidized DAMPs reprogram their metabolism to support redox homeostasis and inflammation through a TLR2-Syk-ceramide dependent mechanism. Mol. Metab. 7, 23-34.

Shah, B. S., Burt, K. G., Jacobsen, T., Fernandes, T. D., Alipui, D. O., Weber, K. T., Levine, M., Chavan, S. S., Yang, H., Tracey, K. J., Chahine N.O., 2019. High mobility group box-1 induces pro-inflammatory signaling in human nucleus pulposus cells via toll-like receptor 4-dependent pathway. J. Orthop. Res. 37, 220-231.

Shamshuddin, N.S.S., Mohd Zohdi, R., 2016. Gelam honey attenuates ovalbumin-induced airway inflammation in a mice model of allergic asthma. J. Tradit. Complement. Med. 8, 39-45.

Shao, D., Oka, S. I., Brady, C. D., Haendeler, J., Eaton, P., Sadoshima, J., 2012. Redox modification of cell signaling in the cardiovascular system. J. Mol. Cell. Cardiol. 52, 550-558.

Shi, N., Clinton, S.K., Liu, Z., Wang, Y., Riedl, K.M., Schwartz, S.J., Zhang, X., Pan, Z., Chen, T., 2015. Strawberry phytochemicals inhibit azoxymethane/dextran sodium sulfate-induced colorectal carcinogenesis in Crj: CD-1 mice. Nutrients 7, 1696-1715.

Shukitt-Hale, B., Lau, F.C., Cheng, V., Luskin, K., Carey, A.N., Carrihill-Knoll, K., Rabin, B.M., Joseph, J.A., 2013. Changes in gene expression in the rat hippocampus following exposure to 56Fe particles and protection by berry diets. Cent. Nerv. Sys.t Agents Med. Chem. 13, 36-42.

Soni, N., Singh, V., Mohammad, S,, Singh, R.K., Pal, U.S., Singh, R., Aggrwal, J., Pal, M., 2016. Effects of honey in the management of alveolar osteitis: A study. Natl. J. Maxillofac. Surg. 7, 136–147.

Squillaro, T., Cimini, A., Peluso, G., Giordano, A., Melone, M.A.B., 2018. Nano-delivery systems for encapsulation of dietary polyphenols: An experimental approach for neurodegenerative diseases and brain tumors. Biochem. Pharmacol. 154, 303-317.

Tahir, A.A., Sani, N.F., Murad, N.A., Makpol, S., Ngah, W.Z., Yusof, Y.A., 2015. Combined ginger extract & Gelam honey modulate Ras/ERK and PI3K/AKT pathway genes in colon cancer HT29 cells. Nutr. J. 14, 31.

Tang, S.P., Kuttulebbai Nainamohamed Salam, S., Jaafar, H., Gan, S.H., Muzaimi, M., Sulaiman, S.A., 2017. Tualang honey protects the rat midbrain and lung against repeated paraquat exposure. Oxid. Med. Cell Longev. 2017, 4605782.

Tanvir, E.M., Afroza, R., Zaman Chowdhury, M.A., Khalil, M.I., Hossain, M.S., Rahman, M.A., Rashid, M.H., Hua Gan, S., 2015. Honey has a protective effect against chlorpyrifos-induced toxicity on lipid peroxidation, diagnostic markers and hepatic histoarchitecture. Eur. J. Integr. Med., 7, 525-533.

Teng, H., Chen, L., 2019. Polyphenols and bioavailability: an update. Crit. Rev. Food Sci. Nutr. 1-12.

Thomas-Valdés, S., Theoduloz, C., Jiménez-Aspee, F., Burgos-Edwards, A., Schmeda-Hirschmann, G., 2018. Changes in polyphenol composition and bioactivity of the native Chilean white strawberry (Fragaria chiloensis spp. chiloensis f. chiloensis) after *in vitro* gastrointestinal digestion. Food Res. Int. 105, 10-18.

Trachootham, D., Lu W., Ogasawara M.A., Nilsa R.D., Huang, P., 2008. Redox regulation of cell survival. Antioxid. Redox Signal. 10, 1343-1374.

Truchado, P., Larrosa, M., García-Conesa, M.T., Cerdá, B., Vidal-Guevara, M.L., Tomás-Barberán, F.A., Espín, J.C., 2012. Strawberry processing does not affect the production and urinary excretion of urolithins, ellagic acid metabolites, in humans. J. Agric. Food Chem. 60, 5749-5754.

Tulipani, S., Romandini, S., Busco, F., Bompadre, S., Mezzetti, B., Battino, M., 2009. Ascorbate, not urate, modulates the plasma antioxidant capacity after strawberry intake. Food Chem. 117, 181-188.

Tulipani, S., Alvarez-Suarez, J.M., Busco, F., Bompadre, S., Quiles, J.L., Mezzetti, B., Battino, M., 2011. Strawberry consumption improves plasma antioxidant status and erythrocyte resistance to oxidative haemolysis in humans. Food Chem. 128, 180–186.

Tulipani, S., Armeni, T., Giampieri, F., Alvarez-Suarez, J.M., Gonzalez-Paramas, A.M., Santos-Buelga, C., Busco, F., Principato, G., Bompadre, S., Quiles, J.L., Mezzetti, B., Battino, M., 2014. Strawberry intake increases blood fluid, erythrocyte and mononuclear cell defenses against oxidative challenge. Food Chem. 156, 87–93.

Tungmunnithum, D., Thongboonyou, A., Pholboon, A., Yangsabai, A., 2018. Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: An Overview. Medicines (Basel). 5, 93.

Uwaydat, S., Jha, P., Tytarenko, R., Brown, H., Wiggins, M., Bora, P., Bora, N.S., 2011. The use of topical honey in the treatment of corneal abrasions and endotoxin-induced keratitis in an animal model. Curr. Eye Res. 36, 787-796.

Wan, S.W.G., Mahaneem, M., Siti, A.S., Aniza, A.A., Harmy, M.Y., 2015. Tualang honey supplementation improves oxidative stress status among chronic smokers. Toxicol. Environ. Chem. 97, 1017-1024.

Waykar, B., Alqadhi, Y., 2019. Royal jelly and honey ameliorates cisplatin induced alterations in biomarker levels of oxidative stress in kidney of rat. Indian J Public Health Res Dev. 10, 1053.

Wen, C.T., Hussein, S.Z., Abdullah, S., Karim, N.A., Makpol, S., Mohd Yusof, Y.A., 2012. Gelam and Nenas honeys inhibit proliferation of HT 29 colon cancer cells by inducing DNA damage and apoptosis while suppressing inflammation. Asian Pac. J. Cancer Prev. 13, 1605-1610.

Włodarczyk, M., Nowicka, G., 2019. Obesity, DNA Damage, and Development of Obesity-Related Diseases. Int. J. Mol. Sci. 20, 1146.

Xiao, J., Liu, Y., Xing, F., Leung, T.M., Liong, E.C., Tipoe, G.L., 2016. Bee's honey attenuates non-alcoholic steatohepatitis-induced hepatic injury through the regulation of thioredoxin-interacting protein-NLRP3 inflammasome pathway. Eur. J. Nutr. 55, 1465-1477.

Yaman, T., Yener, Z., Celik, I., 2016. Histopathological and biochemical investigations of protective role of honey in rats with experimental aflatoxicosis. BMC Complement. Altern. Med. 16, 232.

Yoshizaki, T., Schenk, S., Imamura, T., Babendure, J.L., Sonoda, N., Bae, E.J., Oh, D.Y., Lu, M., Milne, J.C., Westphal, C., Bandyopadhyay, G., Olefsky, J.M., 2010. SIRT1 inhibits inflammatory pathways in macrophages and modulates insulin sensitivity. Am. J. Physiol. Endocrinol. Metab. 298, E419-428.

Zhao, M., Liu, X. Luo, Y., Guo, H., Hu, X., Chen, F., 2015. Evaluation of protective effect of freeze-dried strawberry, grape, and blueberry powder on acrylamide toxicity in mice. J. Food Sci. 80, H869-74.

Zhao, H., Cheng, N., He, L., Peng, G., Xue, X., Wu, L., Cao, W., 2017. Antioxidant and hepatoprotective effects of A. cerana honey against acute alcohol-induced liver damage in mice. Food Res. Int. 101, 35-44.

Zhao, C., Yang, C., Wai, S.T.C., Zhang, Y., Portillo, M., Paoli, P., Wu, Y., San Cheang, W., Liu, B., Carpéné, C., Xiao, J., Cao, H. 2019a. Regulation of glucose metabolism by bioactive phytochemicals for the management of type 2 diabetes mellitus. Crit. Rev. Food Sci. Nutr. 59, 830-847.

Zhao, D., Simon, J.E., Wu, Q., 2019b. A critical review on grape polyphenols for neuroprotection: Strategies to enhance bioefficacy. Crit. Rev. Food Sci. Nutr. 1-29.

Živković, L., Bajić, V., Dekanski, D., Čabarkapa-Pirković, A., Giampieri, F., Gasparrini, M., Mazzoni, L., Potparević, B.S., 2018. Manuka honey attenuates oxidative damage induced by H_2O_2 in human whole blood in vitro. Food Chem. Toxicol. 119, 61-65.

Zunino, S.J., Parelman, M.A., Freytag, T.L., Stephensen, C.B., Kelley, D.S., Mackey, B.E., Woodhouse, L.R., Bonnel, E.L., 2012. Effects of dietary strawberry powder on blood lipids and inflammatory markers in obese human subjects. Br. J. Nutr. 108, 900-909.

Figure legends

Fig. 1. The relationship between inflammatory and oxidative stress. Activation of macrophages and mitochondrial respiration increase ROS production that leads to tissue oxidation and activates cellular signaling pathways MAPKs, PK13, NF-κB and NLRP3 inflammasome. NF-κB upregulates proinflammatory cytokines, COX-2, NOS. TNF-α, IL-6, IL-1 stimulate in turn macrophages and neutrophils for inflammation process. NADPH oxidase and uncoupled NOS are also responsible for ROS production that causes tissue oxidation, necrosis and DNA damage. Necrosis of tissue activates, via TRL4 receptor, HMGB1 that in turn activates NF-κB and NLRP3 inflammasome. Nrf2 play a significant role for NLRP3 activation by upregulating HO-1 and reducing oxidative stress by inhibiting NF-κB signaling and vice versa.

Fig. 2. Schematic representation of the absorption and metabolic processes of the main polyphenols present in strawberry and honey.

Fig. 3. Schematic representation of the effects of strawberry and honey on the main molecular mechanisms involved in inflammation and antioxidant defense. Strawberry and honey are able to modulate the key factors involved in the inflammatory cascade (i.e., NF-κB, Ikk-β, AP-1) and in the antioxidant defense (i.e., Nrf2 and AMPK).

Table 1. Effect of strawberry on oxidative stress.

Experimental Model	Treatments	Main effects	Ref.
In vitro			
Human dermal fibroblasts stressed with (UVA)-radiation	Strawberry extract: 50, 250, 500 μg/mL for 30 minutes	-↑ cell viability -↓ DNA damage	Giampieri et.al., 2012
Human dermal fibroblasts stressed with H_2O_2	Strawberry extract: 500 μg/mL for 24 h	-↑ cell viability -↓ ROS -↓ lipid peroxidation -↓ DNA damage -↑ mitochondrial funtionality -↑ cell regenerative capacity	Giampieri et.al., 2014a
Human dermal fibroblasts stressed with AAPH	Strawberry extract: 500 μg/mL for 24 h	-↑cell viability -↓ ROS -↓ apoptosis -↑ mitochondrial funtionality	Giampieri et.al., 2014b
Human dermal fibroblasts stressed with (UVA)-radiation	Strawberry extract: 50 μg/mL for 1 h	-↓ ROS -↑ catalase, SOD, HO-1 -↑ Nrf2 pathway -↑ mitochondrial funtionality	Gasparrini et.al., 2017a
Human epithelial gastric cells	Strawberry extract: 7.8, 15.6, 31.3, and 62.5 μg/ml for 30 min and 1 h	-↑ citoprotection -↑ glyoxalase I, glutatione-S-transferase -↓ lipid peroxidation	Ávila et al., 2017
HepG2 cells	Strawberry extract: 10, 50, 100 μg/mL for 24 h	-↓ ROS -↓ lipid peroxidation -↑catalase, SOD	Forbes-Hernandezet al., 2017
HepG2 cells stressed with AAPH	Strawberry extract: 25 μg/mL for 24 h	- ↑citoprotection -↓ ROS -↓ apoptosis	Ariza et al., 2018
Human myometrial cells	Strawberry extract: 250 μg/mL for 48 h	-↑ citoprotection -↓ ROS -↓ apoptosis -↑ mitochondrial funtionality	Giampieri et al., 2019
Murine BV-2 microglia stressed with H_2O_2	Strawberry extract: 20 μg/mL for 24 h	-↑ citoprotection -↓ ROS -↓ apoptosis	Ma et al., 2018
Murine adipocytes 3T3-L1	Strawberry extract: 10, 50, 100 μg/mL for 24 h	-↓ ROS	Forbes-Hernandez et al.,

		-↓ lipid peroxidation -↑catalase, SOD	2018
HepG2 cells stressed with AAPH	Digested strawberry extract: 2 µg/mL for 24 h	- ↑citoprotection -↓ ROS -↓ apoptosis	Ariza et al., 2018
Human gastric adenocarcinoma (AGS) cells stressed with H_2O_2	Digested strawberry extract: 125 µg/mL	-↓citoprotection	Thomas-Valdés et al., 2018
In vivo			
24 Wistar rats stressed with doxorubicin	Diet supplemented with 10 % of strawberry powder for 16 weeks	-↓ ROS -↓ DNA damage -↓ lipid peroxidation -↓ protein oxidation -↑ plasma retinol, tocopherol -↑SOD, catalase, GST,GR,GPx -↑GSH -↑mitochondrial funtionality	Diamanti et al., 2014
32 Wistar rats stressed with doxorubicin	Diet supplemented with 15 % of strawberry powder for 8 weeks	-↑ plasma total antioxidant capacity -↓ ROS -↓ DNA damage -↓ lipid peroxidation -↓ protein oxidation -↑ retinol, tocopherol -↑ SOD, catalase, GST,GR,GPx -↑ mitochondrial funtionality -↑ mitochondrial antioxidants	Giampieri et al., 2016
40 Wistar albino rats stressed with carbon tetrachloride	Strawberry juice supplementation for 12 weeks	-↓ lipid peroxidation -↓ NO levels -↑ GSH -↑ SOD, Catalase, GPx -↓ apoptosis	Hamed et al., 2016
32 Wistar rats stressed with cadmium chloride (liver, kidney, brain)	Strawberry methanolic extract: 250 mg/kg	-↓ liver lipid peroxidation -↓ liver NO levels -↑ liver GSH -↑ liver SOD, Catalase, GPx, GR -↓ liver apoptosis	Elkhadragy and Abdel Moneim, 2017; Elkhadragy et al., 2018a, 2018b
36 Wistar rats stressed with ethanol	Strawberry crude extract: 40 mg/kg for 10 days	-↓ lipid peroxidation -↑ SOD, catalase -↓ Ulcer index	Alvarez-Suarez, et al., 2011
Rats exposed to1.5Gy of ^{56}Fe particles	Diet supplemented with 2 % of strawberry powder for	-↑ SOD, GST	Poulose et al., 2014

	8 weeks before and 30 days after irradiation	-↓ NOX2 -↓ iNOS	
20 Wistar rats fed a high-fat diet	Diet supplemented with 0.2 % of strawberryextract	-↓ lipid peroxidation -↓ protein oxidation -↑ GABA levels	Sandoval-Salazar et al., 2019
48 Wistar rats fed a high-fructose diet	Ellagitannin-enriched strawberry extract for 6 weeks	-↑ serum antioxidant capacity -↓ lipid peroxidation -↑GSH	Fotschki al., 2018
50 Kunming mice stressed with acrylamide	Diet supplemented with strawberry powder for 14 days	-↑ liver antioxidant enzymes -↓ DNA damage -↓ reproductive toxicity	Zhao et al., 2015
16 old Wistar rats	Diet supplemented with 15 % of strawberry powder for 8 weeks	-↓ ROS -↓ DNA damage -↓ lipid peroxidation -↓ protein oxidation -↑ SOD, catalase, GST,GR,GPx -↑ mitochondrial functionality -↑ mitochondrial biogenesis -↑ AMPK/Nrf2 pathway	Giampieri et al., 2017b
8 healthy subjects	1 kg of fresh strawberry	-↑ plasma total antioxidant capacity -↑ plasma vitamin C level	Tulipani et al., 2009
23 healthy subjects	500 g of fresh strawberry for 15 days	-↑ plasma total antioxidant capacity -↓ protein oxidation -↓ lipid peroxidation	Romandini et al., 2013
10 healthy volunteers	500 g of fresh strawberry for 9 days	-↑plasma total antioxidant capacity	Prymont-Przyminska et al., 2014
23 healthy subjects	500 g of fresh strawberry for 15 days	-↑ plasma total antioxidant capacity -↓ DNA damage -↓ lipid peroxidation -↓ oxidative hemolysis -↓ number of activated platelets	Alvarez-Suarez et al., 2014
12 healthy individuals	500 g of fresh strawberry for 16 days	-↑ plasma total antioxidant capacity -↑ plasma vitamin C level -↓ oxidative hemolysis	Tulipani et al., 2011
18 healthy individuals	500 g of fresh strawberry for 14 days	-↑ plasma total antioxidant capacity -↑ plasma vitamin C level -↓ lipid peroxidation -↓ oxidative hemolysis -↓ mononuclear cell mortality	Tulipani et al, 2014
21 healthy volunteers	250 g of dried strawberry for 3 weeks	-↓ LDL oxidation	Henning et al., 2010

36 subjects with Type 2 Diabetes	Beverage of freeze-dried strawberry (50g) daily (equivalent at 500g of fresh fruit) for 6 weeks	-↑ plasma total antioxidant capacity -↓ lipid peroxidation	Moazen et al., 2013
93600 women	>3 servings/week, 18 years of follow-up	-↓ myocardial infarction risk	Cassidy et al., 2013

Table 2. Effect of honey on oxidative stress.

Experimental Model	**Treatments**	**Main effects**	**Ref.**
In vitro			
Human diploid fibroblasts subjected to γ-irradiation	Monofloral Gelam honey: 6 mg/ml for 24 h	-↑ antioxidant enzyme expression -↑ antioxidant enzyme activities	Ahmad et al., 2013
Human dermal fibroblasts stressed with AAPH	Manuka honey: 0.1% for 24 h	-↓ apoptosis -↓ ROS -↓ lipid peroxidation -↓ protein oxidation -↑ mitochondrial functionality -↑ AMPK/Nrf2/ARE signalling pathway	Alvarez-Suarez et. al., 2016
HepG2 cells	Bee honey: 5%, 10%, 15%, and 20% for 6-72 h	-↑ total antioxidant status -↓ NO -↓ apoptosis	Hassan et al., 2012
HepG2 cells treated with different food mutagens	Rosemary, heather and heterofloral honeys: 0.1–100 mg/mL for 24 h	-↓ DNA damage	Haza and Morales, 2013
Bone cells were isolated from the rat femur and tibia and treated with hydrocortisone	Bee honey: 0.749 mg/ml for 72 h (IC_{50})	-↓ ROS -↓ lipid peroxidation -↑SOD, Gpx, GSH -↓ NO	Abu-Serie and Habashy, 2018
Red blood cells from healthy volunteers stressed with AAPH	Christmas vine and Linen vine honeys: 10-80 ug/mL for 45 min	-↑hemolysis -↑SOD, GSH -↓ lipid peroxidation	Alvarez-Suarez et al, 2012
Red blood cells from healthy volunteers stressed with AAPH		-↓ lipid peroxidation	García-Tenesaca et al., 2017
Whole blood samples from healthy volunteers	Manuka honey: 25-1000 μg/ml for 30 min	-↓ oxidative DNA damage	Živković et al., 2018
In vivo			
80 Sprague Dawley rats stressed with	Oral dose of honey: 5 g/kg body weight for 4 weeks	-↑ liver and kidney antioxidant capacity	El Denshary et al., 2012

tetrachloride		-↓ lipid peroxidation -↑ DNA content	
24 Wistar rats stressed with tetrachloride	Carob honey: 2 g/kg. body weight for 12 days	-↓ lipid peroxidation -↓ protein oxidation -↑ catalase, GPx, GSH -↓ protein oxidation products	Al-Yahya et al., 2013
Wistar albino rats stressed with tetrachloride	Saudi Sidr honey: 0.5, 1.0 g/kg for 6 weeks	-↓ lipid peroxidation -↓ protein oxidation	Cheng et al., 2015
48 Kunming mice stressed with tetrachloride	Buckwheat honey: 0.22 g/10 g body weight for 10 weeks	-↑ plasma total antioxidant capacity -↓ lipid peroxidation -↑ SOD, GPx -↓ DNA damage	El-Haskoury et al., 2018
24 albino rats treated with ethanol	Manuka honey 7 days before induction of ulcer at a dose of 0.1, 1.0, and 2.5 mg/kg body weight	-↓ mucosa lipid peroxidation -↑ SOD, GPx, GSH -↓ ulcer index	Almasaudi et al., 2016
36 Sprague-Dawley rats treated with acetic acid	Manuka honey: 0.625, 1.25, 2.5 g/kg body weight for 12 days	-↓ mucosa lipid peroxidation -↑ SOD, GPx, GSH -↓ ulcer index -↓ apoptosis	Almasaudi et al., 2017
60 Kunming mice treated with ethanol	*A. cerana* honey: 5, 10, 20 g/kg body weight twice for 12 weeks	-↑ serum total antioxidant capacity -↓ serum lipoprotein oxidation -↓ liver lipid peroxidation -↑ SOD, GPx	Zhao et al., 2017
24 Sprague-Dawley rats treated with streptozotocin (pancreas, kidney)	Tualang honey :1.0 g/kg/body weight for 4 weeks	-↓ lipid peroxidation -↑ catalase, GR, GSH -↑ kidney total antioxidant status	Erejuwa et al., 2010, 2011
40 albino Wistar rats with ulcerative colitis induced by dextran sodium sulphate	5 g/kg of honey orally administrated once/day for 3 weeks	-↑ SOD, GSH	Nooh and Nour-Eldien, 2016
32 Wistar rats with dyslipidaemic diet	Malícia honey: 1000 mg/kg body weight for 35 days	-↑ SOD, GPx -↑ glucose tolerance -↓ serum total cholesterol, LDL, AST	Bezerra et al., 2018
20 Wistar rats treated with sodium arsenite	Acacia honey: 20% at 5 mL/kg body weight for 1 week	-↑ SOD, catalase, GPx -↓ lipid peroxidation	Aliyu et al., 2013
60 Wister rats treated with diethyl nitrosamine	Bee honey: 2 g/day for 6 months	-↑ catalase, GPx, GST, GSH -↓ lipid peroxidation	Naima et al., 2016
32 Wister rats treated with isoproterenol	Sundarban honey: 5 g/kg for 6 weeks	-↑ SOD, GPx, GR -↓ lipid peroxidation -↓ LDL	Afroz et al., 2016
24 Wister rats treated with cisplatin	Honey: 500 mg/kg body weight for 15 days	-↓ lipid peroxidation	Waykar and Alqadhi,

		-↑ catalase, SOD, GPx, GR, GSH	2019
18 Sprague–Dawley rats treated with aflatoxin	Honey: 1 mL/kg by gavage for 90 days	-↓ lipid peroxidation -↑ catalase, SOD, GPx, GR, GSH	Yaman et al., 2016
60 Swiss mice treated with ochratoxin A	Honey: 2 g/kg body weight for 15 days	-↓ DNA damage	Oršolić et al., 2017
48 BALB/c mice treated with trichlorfon	Pine honey: 1 g/kg body weight for 21 days	-↑ catalase, SOD, GPx -↓ lipid peroxidation	Eraslan et al., 2010
24 Wistar rats treated with chlorpyrifos	Multi-floral honey: 3 g/kg body weight for 28 days	-↓ lipid peroxidation	Tanvir et al., 2015
18 Rattus norvegicus treated with tartrazine	Sidr bee honey: 2.5 g/Kg body weight for 18 weeks	-↑ catalase, SOD, GR, GSH -↓ lipid peroxidation	El Rabey et al., 2019
24 Wistar rats treated with lead acetate	Unilorin honey: 1 mg/kg body weight for 28 days	-↑ SOD, GST, GSH	Abdulmajeed et al., 2016
90 Sprague–Dawley rats treated with kainic acid	Tualang honey: 1 g/kg body weight for five times every 12 h	-↓ lipid peroxidation -↑ total antioxidant status	Mohd Sairazi et al., 2017
75 rats treated with paraquat	Tualang honey: 1 g/kg body weight for 4 weeks	-↓ lipid peroxidation -↑ SOD	Tang et al., 2017
64 chronic smokers	Tualang honey: 20 g/day for 12 weeks	-↑ total antioxidant status -↑ catalase, GPx -↓ F_2-isoprostane	Wan et al., 2015
20 female athletes	Tualang honey: 0.75-1.5 g/kg body weight	-↑ plasma total antioxidant capacity -↓ lipid peroxidation -↓ ROS levels	Ahmad et al., 2017
38 healthy road cyclists	70 g of natural unprocessed honey dissolved in 250 mL distilled water	-↓ lymphocytes DNA damage -↓ peroxidative biomarkers -↑ total antioxidant status	Hajizadeh Maleki et al., 2016

Table 3. Effect of strawberry on inflammation.

Experimental Model	Treatments	Main effects	Ref.
In vitro			
Peritoneal macrophages from BALB/cByJNarl mice (6 weeks old) stressed with LPS	Strawberry polysaccharides extract: 250, 500, and 1000 μg/mL for 48 h	-↓IL-1β -↓IL-6 -↑IL-10	Liu and Lin, 2012
RAW 264.7 macrophages stressed with LPS	Strawberry extract: 100 μg/mL for 24 h	-↓NF-KB pathway -↓iNOS -↓TNF-α -↓pIkBα -↓NO -↑Nrf2-AMPK pathway	Gasparrini et.al., 2017b
Human dermal fibroblasts stressed with LPS	Strawberry extract: 100 μg/mL for 24 h	-↓NF-KB pathway -↓pIkBα -↓TNF-α -↓IL-6 -↓IL-1β	Gasparrini et.al., 2018a
Human dermal fibroblasts stressed with (UVA)-radiation	Strawberry extract: 50 μg/mL for 1 hour	-↓pIkBα -↓NF-KB pathway -↓TNF-α -↓IL-6 -↓IL-1β	Gasparrini et.al., 2017a
Human adenocarcinoma cells (CRL-1739) infected with *H.pylori*	Strawberry extract digested *in vitro*: 10 μg/mL for 48 h	-↓NF-KB pathway -↓IL-8 -↓TNF-α	Fumagalli et al., 2016
Platelets isolated from volunteers and subjected to an *in vitro* aggregation with ADP and arachidonic acid	Strawberry extract: 0.1–1 mg/ml for 15 minutes	-↓IL-1β -↓CD40L -↓RANTES	Alarcòn et al., 2015
In vivo			

36 C57BL/6J mice with diet-induced obesity	Diet supplemented with 2-6 % of strawberry powder for 24 weeks	-↓CRP -↓TNF-α -↓IL-6	Parelman et al., 2012
48 Wistar rats	Supplementation in the diet with a 6 % w/w of a freeze-dried strawberry-blueberry (5:1) for 8 weeks	-↓MCP-1 -↓insuline-resistance	Aranaz et al., 2017
60 CD-1 mice with colitis induced by dextran sulfate sodium	Supplementation in the diet with a 2.5% or 5% (w/w) of whole strawberries for 7 days	-↓number of pro-inflammatory immune cells -↓TNF-α -↓IL-1β -↓IL-17 -↓NF-KB pathway -↓COX2 -↓iNOS -↓c-JUN	Han et al., 2019
50 Crj: CD-1 (ICR) mice with colon cancer induced by azoxymethane	Supplementation in the diet with 2.5%, 5% or 10% lyophilized strawberries for 20 weeks	-↓TNF-α -↓IL-1β -↓IL-6 -↓COX2 -↓iNOS	Shi et al., 2015
20 Sprague-Dawley rats radiated with 1.5 Gy or 2.5 Gy of 1 GeV/n ^{56}Fe	Supplementation in the diet with 2 % of strawberry extract for 8 weeks	-↓COX2 -↓NF-KB	Shukitt-Hale et al., 2013
Swiss mice with carrageenan-induced pleuritis	100–400 mg/kg of strawberry fruit crude extract by the oral route	-↓leukocytic infiltrate -↓TNF-α -↓IL-6 -↓NO -↓MPO	Duarte et al., 2018
Healthy subjects 20–50 years old with a BMI of 30–40 kg/m^2	Four servings (80 g for each serving)/day for 7 weeks	-↓IL-1β -↓IL-6 -↓TNF-α -↓CRP	Zunino et al., 2012
26 overweight and obese patients	Strawberry beverage contained 10g/serving of freeze-dried strawberry powder (~100 g fresh strawberries)/day for 6 weeks	-↓IL-1β -↓IL-6 -↓TNF-α -↓CRP	Ellis et al., 2011
36 subjects with Type 2 Diabetes	Beverage of freeze-dried strawberry (50g) daily (equivalent at 500g of fresh fruit) for 6 weeks	-↓CRP -↓MDA	Moazen et al., 2013
17 obese adults with knee osteoarthritis	50 g of strawberry powder for 12 weeks	-↓TNF-α -↓IL-6 -↓IL-1β -↓MMP-3	Schell et al., 2017; Basu et al., 2018

Table 4. Effect of honey on inflammation.

Experimental Model	Treatments	Main effects	Ref.
In vitro			
RAW 264.7 macrophages stressed with LPS	Manuka honey 3-8 mg/mL for 24 h	-↓TNF-α -↓IL-1β -↓IL-6 -↓iNOS	Gasparrini et al., 2018b
RAW 264.7 macrophages stressed with LPS	Manuka honey 1-10 mg-mL for 24 h	-↓p-p38 -↑p-AMPK	Afrin et al., 2018b
RAW 264.7 macrophages stressed with LPS and IFN-γ	Gelam honey 0.039-5 mg/mL for 24 h	-↓peroxynitrite	Kassim et al., 2012a
Human keratinocytes exposed to TNF-α	Fir honey 0.1-5 mg/mL for 24 h	-↓MMP-9	Majtan et al., 2013
Murine epidermal keratinocyte cell line PAM212 stressed with (UVB)-radiation	1% of Tualang honey in the culture medium for 30 min or 24 h	-↓degradation of IκBα -↓IL-1β -↓IL-6 -↓TNF-α -↓COX2 -↓PGE2	Ahmad et al., 2012
Human colorectal adenocarcinoma cell line HT29 stressed with H_2O_2	Gelam honey: 39 and 60 mg/mL for 24 h Nenas honey: 85 and 112.5 mg/mL for 24 h	-↓PGE2	Wen et al., 2012
Human colorectal adenocarcinoma cell line HT29	Gelam honey 20–100 mg/mL for 24 h	-↓NF-KB	Tahir et al., 2015
Human gastric adenocarcinoma AGS cell line infected with *H.pylori*	1.25 % of Manuka honey in the culture medium for 24 h	-↓IL-8	Keenan et al., 2012
Hamster pancreatic cells HIT-T15 cells subjected to an excess of glucose	Gelam honey extract 20, 40, 60, and 80 μg/mL for 24 h	-↓p-JNK -↓Ikk-β -↓TNF-α -↓IL-1β -↑p-Akt	Safi et al., 2016
In vivo			

36 Sprague Dawley stressed with LPS	Injection of 60 mg/kg, 300 mg/kg and 600 mg/kg of extract of Gelam honey diluted in 1 mL of saline solution	-↓IL-10 -↓IL-6 -↓IL-1β -↓TNF-α -↓HMGB1	Kassim et al., 2012b
36 Sprague-Dawley stressed with LPS	4.6 g/kg or 9.3 g/kg dissolved in distilled water with oral gavage for 30 days and dissolved in saline solution for intraperitoneal injection 3 times/week for 28 days	-↓NF-KB p65 -↓MAPK p38 -↑Nrf2	Ranneh et al., 2019
36 New Zealand white rabbits stressed with LPS	500 mg/kg of Gelam honey diluted in saline solution injected before LPS treatment	-↓infiltration of neutrophils -↓MPO activity	Kassim et al, 2012c
30 C57BL/6 mice with ear edema induced by TPA and arachidonic acid	n.a	-↓inflammation level -↓infiltration of neutrophils	Leong et al., 2012
Swiss mice with ear edema induced by TPA	Topical application of the *M. marginata* honey extract: 1.0 mg/ear	-↓inflammation level -↓infiltration of neutrophils -↓MPO activity	Borsato et al., 2014
30 Sprague Dawley rats with paw edema induced by carrageenan and LPS	Injection of Gelam honey: 800 mg/kg in 500 μL of saline solution Injection of Gelam honey extract: 180 mg/kg in 5% DMSO in 500 μL of saline solution 1 h before to induce paw edema	-↓PGE2 -↓intensity and pain of edema	Kassim et al., 2010
30 albino rats with paw edema induced by formalin and carrageenan	Honey orally administered: 200-600 mg/kg of honey	-↓inflammation level -↓intensity and pain of edema	Owoyele et al., 2014
84 Sprague-Dawley rats with paw edema induced by carrageenan	Gelam honey orally administrated prior the induction of edema (1 or 2 g/kg of body weight) for 1 or 7 days	-↓TNF-α -↓IL-6 -↓COX2 -↓iNOS -↓nuclear translocation of NF-κB -↓cytosolic degradation of IkBα	Hussein et al., 2012; Hussein et al., 2013
32 rats with produced intraoral wounds	Cotton swab was soaked in honey and packed into the wound (application for 2,4,6 or 8 days)	-↓wounds size -↓infiltration of neutrophils and leukocytes	Chamani et al., 2017
21 Albino rats (Wistar strain) with ulcers caused by a second degree burn	Topical application of honey twice a day in the first week with intervals of 12 hours, once a day in the second week, followed by alternate days in the third and fourth weeks.	-↓wounds size -↓infiltration of neutrophils and leukocytes	Farzadinia et al., 2016
10 naive Lewis rats with produced corneal abrasion and keratitis	Raw honey topically applied three times a day to one eye of each rat for 48 or 72 h	-↓TGF-β -↓IL-12 -↓TNF-α -↓IFN-γ	Uwaydat et al., 2011

30 adult guinea pigs with conjunctivitis induced by *Pseudomonas aeruginosa* or *Staphylococcus aureus*	1 drop of raw Stingless bee honey twice/day for 14 days	-↓inflammation level -↓duration of infection -↓resolution time	Ilechie et al., 2012
48 Sprague-Dawley rats with induced cecal abrasion	Peritoneally application of pectin honey hydrogel (1:1:1)	-↓inflammatory parameters -↓formation of post-surgical abdominal adhesion	Giusto et al., 2017
40 rabbits with ovalbumin induced asthma	Aerosolized honey at 25% (v/v) and 50% (v/v) in sterile phosphate buffer saline for five consecutive days	-↓cell-mediated inflammatory response -↓infiltration of eosinophils in the airways	Kamaruzaman et al., 2014
36 albino CD1 mice with conalbumin induced asthma	650 mg/kg honey once per day for 18 consecutive days	-↓inflammatory parameters	El-Aidy et al., 2015
42 Balb/c mice sensitized with ovalbumin	Oral gavage with 10%, 40%, 80% (v/v) of honey diluted in PBS once a day for 5 days (	-↓infiltration of inflammatory cells in the lung tissue	Shamshuddin and Mohd Zohdi, 2016
Adult Sprague-Dawley rats with induced diabetes by streptozotocin nicotinamide	Stingless bee honey at 1 and 2 g/kg/b.w. given orally for 28 days	-↓Ikk-β in pancreatic islets -↓IL-1β -↓TNF-α -↓NF-KB	Aziz et al., 2017
18 Sprague–Dawley rats with induced non-alcoholic steatohepatitis	5 g/kg of honey intragastrically administrated for 8 weeks	-↓activation of NLRP3 inflammasome -↓TXNIP -↓TNF-α -↓IL-6 -↓IL-1β -↓IL-18	Xiao et al., 2016
40 albino Wistar rats with ulcerative colitis induced by dextran sodium sulphate	5 g/kg of honey orally administrated once/day for 3 weeks	-↓inflammatory parameters -↓IL-6 -↓IL-1β -↓TNF-α -↓inflammatory cell infiltration	Nooh and Nour-Eldien, 2016
Old C57BL/6 mice exposed to cisplatin	Oral feeding of crude honey (500mg/kg BW per day) for 3 days after treatment with cisplatin	-↓infiltration of neutrophils in the kidneys -↓TNF-α -↓MCP-1 -↓IL-1β -↓IL-6 -↓NF-KB -↑AMWAP	Hamad et al., 2015
46 patients with chronic rhinosinusitis	Inhalation of saline solution with 5% or 7% of Manuka honey twice-daily for twelve weeks	-↓IL-6 -↓IL-8 -↓IL-13 -↓MCP-1	Manji et al., 2018

		-↓MIP-1β	
64 patients with chronic rhinosinusitis	Thyme honey nasal spray with 35 % w/v honey	-↓inflammatory parameters -↓synechiae formation -↓epistaxis	Hashemian et al., 2015
80 women diagnosed with vulvovaginal candidiasis	Topical application of honey and a neutral cream in a 70:30 ratio once/day for 7 days	-↓inflammatory parameters	Banaeian et al., 2017
36 patients suffering from different wound-healing disorders in the head and neck area	n.a.	-↓inflammatory parameters	Knipping et al. 2012
100 patients with superficial thermal burns involving less than 40%	Undiluted honey topically applied in quantities of 16-30 ml, depending on the size of the burn daily for 21 days	-↓inflammatory parameters	Maghsoudi et al., 2011
50 patients with alveolar osteitis	Honey dressing changed daily for the first 2 days and then alternatively for the others 13 days	-↓inflammatory parameters	Soni et al., 2016
28 patients with diagnosed open mastoid cavity	Medical honey gel application for 12 weeks	-↓inflammatory parameters	Henatsch et al., 2015
10 experienced male soccer players	Beverage with honey (0.5 g/kg) 30 min before the start of the exercise test and at the 10-min halftime	-↓IL-6 -↓IL-10	Abbey and Rankin, 2009

Graphical abstract