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

3  
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30 **Abstract**

31 **Background**

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

39

40 **Purpose**

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

44

45 **Methods**

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

50

51 **Results**

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

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

60

## 61 **Conclusions**

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

68

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

## 70 **Abbreviation**

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

90

91

## 92 **Introduction**

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

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

118 consumption has been associated with a lower risk of chronic-degenerative diseases (Afrin et al.,  
119 2016, 2018a; Giampieri et al., 2017a; Cianciosi et al., 2018). The aim of the present review is to  
120 summarize scientific evidence, obtained from *in vitro* and *in vivo* studies during the last 10 years, on  
121 the antioxidant and anti-inflammatory potential of strawberry and honey bioactive compounds in  
122 the prevention of the most common pathologies, with particular attention to their metabolism and  
123 bioavailability.

124

### 125 **Cross talk between oxidative stress and inflammation in health and disease**

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

129 The main cellular sources of ROS are nicotinamide adenine dinucleotide phosphate hydrogen  
130 (NADPH) oxidases (NOXs) and mitochondria, throughout the mitochondrial electron transport  
131 chain (METC) (Dunn et al., 2015), while the main factors that promote chronic inflammation are  
132 excessive production of oxidative stress, proinflammatory cytokines, altered metabolism of adipose  
133 tissue and chronic infections (Mihai et al., 2018). During inflammation,  $O_2^{\cdot-}$  is formed by xanthine  
134 dehydrogenase, during METC, in the endoplasmic reticulum (ER), or from different NOXs by  
135 enzymatic pathways and uncoupled nitric oxide synthase (NOS), while nitric oxide ( $NO^{\cdot}$ ) is  
136 produced from l-arginine and molecular oxygen ( $O_2$ ) by the activity of various NOS; simultaneous  
137 generation of  $NO^{\cdot}$  and  $O_2^{\cdot-}$  immediately produces peroxynitrite ( $NO_3^-$ ) (Lugrin et al., 2014), which  
138 sustains the production of ROS (Forstermann and Li, 2011).

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

144 al., 2019). Also metabolic and bioenergetic alterations may modulate macrophages activities,  
145 promoting an increase in tissue phospholipid oxidation (Serbulea et al., 2018) and a consequent  
146 modification of membrane properties, as well as a stimulation of inflammation (Parra-Ortiz et al.,  
147 2019). Besides this, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-6 and other proinflammatory  
148 molecules, such as cyclooxygenase (COX)-2, NOS, superoxide, ROS and NO, are secreted from  
149 activated macrophages that may damage DNA by oxidation (Włodarczyk and Nowicka, 2019). In  
150 addition, ROS generation in adipocytes stimulates pro-inflammatory adipokines and perpetuates  
151 chronic inflammation in the target tissue (Fig. 1) (Parra-Ortiz et al., 2019).

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

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

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

187

## 188 **Metabolism and bioavailability of dietary polyphenols**

### 189 *General aspects*

190 The role of polyphenols in the prevention and/or treatment of several chronic diseases has been  
191 emphasized in the last years (Chen et al., 2018b; Cao et al., 2019; Zhao et al., 2019a). The health  
192 benefits of these compounds range from antioxidant and free radicals scavenging effects to anti-  
193 inflammatory, anticarcinogenic or cardioprotective properties. However, it is known that they are  
194 poorly absorbed and/or extensively metabolized by phase I/II enzymatic reactions reaching the  
195 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  $\beta$ -hydrolysis. This step is  
216 primarily mediated by the lactase phlorizin hydrolase (LPH) and the  $\beta$ -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).

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

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

236 The conjugated forms that return into the intestine, together with the remaining unmodified  
237 polyphenols (generally, multimeric polyphenols), are metabolized by gut microbial enzymes before  
238 being reabsorbed again. Such enterohepatic circulation contributes to increase the level and the half-  
239 life of flavonoids in the plasma (Murota et al., 2018). It has been estimated that approximately 90-  
240 95% of the dietary polyphenols are not absorbed in the small intestine and pass directly to the colon  
241 (Olivero-David et al., 2019). Finally, the metabolites that are not absorbed are eliminated via feces  
242 (Marín et al., 2015; Santhakumar et al., 2018; Kawabata et al., 2019) (Fig. 2).

243

#### 244 *Strawberry and honey polyphenols*

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

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

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

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

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

279 Regarding honey, the main class of polyphenols of this matrix are flavonoids, that are present  
280 mainly as aglycones, because of the presence of some glucosidases deriving from the salivary  
281 glands of bees, which contribute to hydrolyze these compounds, increasing their bioavailability.  
282 Once absorbed from the intestinal epithelium, these compounds are subjected to the second phase of  
283 the metabolism, that gives rise to many metabolites, such as sulfonated-, gluconated and methylated  
284 products by different types of enzymes, including sulfotransferases, glucuronosyltransferases and  
285 methyltransferases. These metabolites enter the third phase of the metabolism, where some proteins  
286 associated with multi-resistance (MRP1, MRP2, MRP3) transport flavonoids back into the intestinal  
287 lumen, inside the blood cells or in the hepatocytes through the portal venous system. Finally, the  
288 glycosided flavonoids, that are resistant to LPH or CBG action, are not absorbed from the small  
289 intestine, but are deglycosylated by the microbiota of colon into different derivates that can be  
290 absorbed by the liver and be further conjugated or can be excreted with the feces. To the best of our  
291 knowledge, only one study has evaluated the bioavailability of honey in humans: in plasma of 40  
292 healthy volunteers consuming 1.5 mg/kg of buckwheat honey, the total antioxidant capacity and the  
293 total phenolic content increased 2 h after honey supplementation and remained high for 6 h,  
294 suggesting that the bioavailability of these phenolic compounds is rather high (Schramm et al.,  
295 2003).

296

297

298

299 **Factors that impact dietary polyphenols bioavailability**

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

304

305 *Structure and stability*

306 Chemical structure of polyphenols is a critical factor affecting their bioavailability. In food  
307 matrices, they can be found as glycosylated forms, aglycones or polymers (Olivero-David et al.,  
308 2019). The hydroxylation degree, methoxylation, as well as the hydrogenation of the double bond  
309 between C2 and C3, significantly influence the stability of flavonoids, the main family of dietary  
310 polyphenols. The stability of non-flavonoid polyphenols is also influenced by the hydroxylation  
311 degree (Luca et al., 2019).

312 As explained above, most dietary polyphenols cannot be absorbed in their native form and  
313 experience a series of transformations by intestinal enzymes or colonic microbiota (Olivero-David  
314 et al., 2019). Polymerization degree significantly influences the cellular uptake of polyphenols (Hu  
315 et al., 2017): for example, polymeric compounds, such as proanthocyanidins that are typical phenols  
316 of strawberry, have greater difficulty for being absorbed in the small intestine and are poorly  
317 degraded by the colonic microbiota due to the complexity of their structure (Olivero-David et al.,  
318 2019). In that sense, it has been shown that absorption of dimers of procyanidins is much lower  
319 (<1%) than absorption of monomers as epicatechin, which is around 45% (Hu et al., 2017).

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

324 Regarding the stability, the gastric acid conditions (pH range between 2-4) favor polyphenols  
325 stability, while the alkaline conditions of the intestine (up to pH~7.4) contribute to their degradation  
326 (Hu et al., 2017; Squillaro et al., 2018), leading to a low overall uptake into bloodstream (Hu et al.,  
327 2017).

328

### 329 *Solubility*

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

335 It could be thought that polyphenols with greater solubility would have a higher bioavailability,  
336 however, this idea is not completely true, since it underestimates the important role of intestinal cell  
337 membrane permeability. According to their solubility and cell membrane permeability, dietary  
338 polyphenols can be classified into three main categories: (i) high solubility with poor cell membrane  
339 permeability; (ii) low solubility and poor cell membrane permeability; and (iii) low solubility with  
340 high cell membrane permeability (Hu et al., 2017; Squillaro et al., 2018). It is accepted that the best  
341 absorbed compounds by the biological systems are those that dissolve well in the two phases, that  
342 means compounds with a lipid/H<sub>2</sub>O partition coefficient approximate or equal to 1, because they  
343 can pass from the external medium to the membrane and from this to the internal aqueous cell  
344 medium.

345

### 346 *Effects of food matrices*

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

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

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

358

### 359 *Interactions with gut microbiota*

360 Microbial degradation is an important factor influencing bioavailability of dietary polyphenols (Liu  
361 et al., 2018). Approximately 90% of consumed polyphenols reach the colon and are transformed  
362 into bioavailable products by the resident microbiota (Pasinetti et al., 2018). The gut microbiota -  
363 defined as diverse bacteria that form symbiotic relationships with their hosts- is responsible for  
364 numerous biotransformation of phenolic compounds thanks to the action of several enzymes,  
365 including glucuronidases, glycosidases, amidases, sulfatases, and esterases. This enzymatic  
366 diversity allows the rupture of complex structures of polyphenols into different metabolites with  
367 low molecular weight, which are more easily absorbable (Murota et al., 2018; Santhakumar et al.,  
368 2018).

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

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

379  
380 *Other factors*

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

388  
389 **Strawberry and honey in oxidative stress**

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

395 *Strawberry and oxidative stress*

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



402 enzymes through Nrf2 pathway activation (Fig. 3) (Giampieri et al., 2012; Giampieri et al., 2014a,  
403 2014b; Gasparrini et al., 2017a). Same favorable effects were found in gastric and hepatic cells  
404 (Ávila et al., 2017; Forbes-Hernández et al., 2017; Ariza et al., 2018), in myometrial cells  
405 (Giampieri et al., 2019), in BV-2 microglia cells (Ma et al., 2018) and in adipocytes (Forbes et al.,  
406 2018), where strawberry extracts exerted cytoprotective effects, by decreasing oxidative stress and  
407 preventing cell death, thanks to high concentrations of their bioactive compounds.

408 To the best of our knowledge, only two studies have evaluated the antioxidant effects of strawberry  
409 after an *in vitro* digestion process, with opposite results. On one side, digested strawberry and  
410 achenes extracts were able to reduce the oxidative damage induced by AAPH in HepG2, decreasing  
411 the intracellular ROS accumulation and apoptosis rate, in a greater extent with respect to raw  
412 strawberry extract, suggesting that the bioactivity of strawberry polyphenols is maintained during  
413 the digestion process (Ariza et al., 2018). On the other side, a decrease in the antioxidant properties  
414 and bioactivity was highlighted after an *in vitro* digestion process of white strawberry in human  
415 epithelial gastric cells AGS treated with H<sub>2</sub>O<sub>2</sub>, suggesting that further studies are needed to  
416 completely comprehend the stability and activity of strawberry digested polyphenols (Thomas-  
417 Valdes et al., 2018).

418 The results obtained *in vitro* have been confirmed in studies performed in *in vivo* models, that  
419 demonstrated the effects of strawberry against oxidative stress, both in physiological and  
420 pathological conditions (Table 1). For example, in rats, strawberry consumption has shown to  
421 reduce doxorubicin-, cadmium chloride- or tetrachloride-induced oxidative damage in plasma,  
422 liver, kidney and brain, by decreasing ROS production and oxidative biomarkers levels, restoring  
423 the antioxidant enzyme activities, ameliorating the mitochondrial antioxidant status and  
424 functionality, alleviating histopathological damage, restoring hemoglobin levels, red blood and  
425 bone marrow cell counts and reducing apoptosis (Diamanti et al., 2014; Giampieri 2016; Hamed  
426 2016; Elkhadragey and Abdel Moneim 2017; Elkhadragey et al., 2018a, 2018b). At the same time, in  
427 rats stressed with ethanol, strawberry consumption was effective in protecting gastric mucosa from

428 ulcerations and erosions by decreasing ROS, enhancing antioxidant defense system and reducing  
429 lipid peroxidation (Alvarez-Suarez et al., 2011). Similar results were found also in rats exposed to  
430 <sup>56</sup>Fe particles (Poulose et al., 2014), in obese rats fed a high-fat (Sandoval-Salazar et al., 2019) or a  
431 high-fructose (Fotschki et al., 2018) diet and in mice stressed with acrylamide (Zhao et al., 2015). In  
432 addition, strawberry intake was effective also in slow-downing the progression of aging in old rats,  
433 by decreasing oxidative stress and ROS production, enhancing antioxidant defense and stimulating  
434 mitochondrial biogenesis and functionality through the activation of the AMP-activated protein  
435 kinase (AMPK) and Nrf2 signaling pathways (Fig. 3) (Giampieri et al., 2017b).

436 Many human studies have been performed in different groups of population, such as healthy  
437 subjects, obese subjects and subjects affected by metabolic syndrome or type 2 diabetes. In most of  
438 cases, strawberry consumption significantly enhanced total antioxidant capacity and vitamin C  
439 concentration in plasma (Tulipani et al., 2009; Romandini et al., 2013; Prymont-Przyminska et al.,  
440 2014; Alvarez-Suarez et al., 2014), increased erythrocytes resistance to hemolysis, augmented the  
441 metabolic activity in mononuclear cells (Tulipani et al., 2011; Tulipani et al., 2014), decreased lipid  
442 peroxidation and ox-LDL (Henning et al., 2010; Tulipani et al., 2011; Cassidy et al., 2013; Moazen  
443 et al., 2013), thus improving antioxidant status and decreasing risk factors for atherosclerosis, type 2  
444 diabetes mellitus and metabolic syndrome.

445

#### 446 *Honey and oxidative stress*

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

454 protected against dietary mutagen-induced DNA damage (Hassan et al., 2012; Haza and Morales,  
455 2013), in rat bone cells with hydrocortisone-induced osteoporosis, where bee honey, in combination  
456 with Greek *Thymus vulgaris* extract, ameliorated the activity of antioxidant enzymes and decreased  
457 the levels of intracellular ROS, NO and lipid peroxidation (Abu-Serie and Habashy, 2018) and in  
458 blood cells, where different types of honeys prevented the oxidative DNA damage, the peroxidation  
459 of lipid membrane, the reduction of intracellular glutathione (GSH) and superoxide dismutase  
460 (SOD) and thus cell hemolysis (Alvarez-Suarez et al, 2012; García-Tenesaca et al., 2017; Živković  
461 et al., 2018).

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

480 Similar trends were found in rats treated with sodium arsenite (Aliyu et al., 2013), diethyl  
481 nitrosamine (Naima et al., 2016), isoproterenol (Afroz et al., 2016) and cisplatin (Waykar and  
482 Alqadhi, 2019), where induced-oxidative stress was efficiently counteracted by honey consumption  
483 through the increase in GSH, SOD, catalase, glutathione transferase (GST), glutathione peroxidase  
484 (GPx) activities and a concomitant decrease in lipid peroxidation in liver, heart and kidney samples.  
485 Honey consumption is effective also in combating the oxidative stress induced by different kind of  
486 contaminants or additives. For example, in rats and mice exposed to aflatoxin (Yaman et al., 2016),  
487 ochratoxin A (Oršolić et al., 2017), trichlorfon (Eraslan et al., 2010), chlorpyrifos (Tanvir et al.,  
488 2015), tartrazine (El Rabey et al., 2019), honey supplementation was able to reduce lipid  
489 peroxidation, DNA damage and to increase enzymatic and non-enzymatic antioxidants in liver and  
490 kidney samples. Similar results were found in brain tissues of rats exposed to different neurotoxic  
491 agents, such as lead acetate (Abdulmajeed et al., 2016), kainic acid (Mohd Sairazi et al., 2017) and  
492 paraquat (Tang et al., 2017), in which honey supplementation, by counteracting oxidative stress,  
493 improved cognitive deficit, reduced neurodegeneration and ameliorated the toxic-induced effects.  
494 Studies performed in humans are very few (Table 2). In female athletes and in chronic smokers,  
495 Tualang honey consumption was effective in promoting an increase in postprandial antioxidant  
496 activity and in reducing oxidative stress after 1-2 hours of consumption (Wan et al., 2015; Ahmad et  
497 al., 2017), while in male road cyclists honey supplementation decreased oxidative stress and  
498 lymphocyte DNA damage and increased antioxidant defense after moderate-to-intensive exercise  
499 training (Hajizadeh Maleki et al., 2016).

500

### 501 **Strawberry and honey in inflammation**

502 As mentioned, the causes of inflammation can be different, including endotoxins, viruses, variation  
503 in fatty acid levels, growth factors, imbalance in the oxidative state, but also oncogenic processes,  
504 excess body fat and a poor diet (Giampieri et al., 2017a). For this reason, a balanced diet, rich in  
505 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-1 $\beta$  and IL-6) and an increase in anti-inflammatory  
514 ones, such as IL-10, by downregulating the NF- $\kappa$ B signalling pathway, reducing inducible NOS  
515 (iNOS), TNF- $\alpha$  and phospho-inhibitory subunit of NF- $\kappa$ B $\alpha$  (pIkB $\alpha$ ) 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<sub>10</sub> was able to protect cells against damage by decreasing inflammatory  
520 markers (pIkB $\alpha$ , NF- $\kappa$ B, TNF- $\alpha$ , IL-1 $\beta$  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- $\kappa$ B signalling pathway and to decrease the secretion of IL-8 and the levels of  
526 TNF- $\alpha$ , IL-1 $\beta$ , 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- $\alpha$   
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- $\alpha$ , IL-1 $\beta$ , IL-17, and in downregulating the  
541 NF- $\kappa$ B 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  $^{56}\text{Fe}$ , strawberries consumption was also able to  
544 improve the neuronal inflammation by decreasing the levels of COX-2 and NF- $\kappa$ B (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- $\alpha$ , 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-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$  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- $\alpha$ , IL- 6, IL-1 $\beta$  and matrix metalloproteinase  
556 (MMP)-3 (Schell et al., 2017; Basu et al., 2018).

557

558 *Honey and inflammation*

559 In the last few years, the evaluation of anti-inflammatory activities of honey has been performed in  
560 several *in vitro* and *in vivo* models (Table 4). For example, in macrophages treated with LPS,  
561 Manuka and Gelam honeys were able to decrease the main inflammatory markers, such as iNOS,  
562 TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and p-38, by inhibiting the TLR4/NF- $\kappa$ B pathway and concomitantly  
563 stimulating that of AMPK (Fig. 3) (Yoshizaki et al., 2010; Kassim et al., 2012a; Afrin et al., 2018b;  
564 Gasparrini et al., 2018b). At the same time, in keratinocytes treated with TNF $\alpha$  or with UVB rays,  
565 Fir and Tualang honeys reduced the expression of metalloprotease, pro-inflammatory cytokines (IL-  
566 1 $\beta$ , IL-6 and TNF $\alpha$ ) and mediators (COX-2 and prostaglandin E2 (PGE2)), by inhibiting NF- $\kappa$ B  
567 translocation and I $\kappa$ B $\alpha$  degradation (Fig. 3), confirming the efficiency of honey in wound healing  
568 treatment (Ahmad et al., 2012; Majtan et al., 2013).

569 Together with oxidative stress, inflammation is the basis of several common chronic-degenerative  
570 diseases, as cancer and metabolic diseases. In HT-29 cells, Nenas and Gelam honeys treatment was  
571 able to downregulate the expression of NF- $\kappa$ B and up-regulate that of I $\kappa$ B $\alpha$ , exerting similar effects  
572 of common anti-inflammatory drugs (Wen et al., 2012; Tahir et al., 2015), while in AGS cells of  
573 gastric human carcinoma, infected with *H. pylori*, and in hamster pancreatic cells Manuka and  
574 Gelam honeys improved the chronic inflammatory state, by decreasing the expression TNF- $\alpha$ , IL-  
575 1 $\beta$ , IL-8, p-JNK and I $\kappa$ B Kinase  $\beta$  and increasing those of p-Akt (Keenan et al., 2012; Zafi et al.,  
576 2016).

577 Many studies performed in *in vivo* models have confirmed the anti-inflammatory effects of honey  
578 (Table 4). For example, in rats and rabbits stressed with LPS, Gelam and stingless bee honeys were  
579 able to reduce the levels of cytokines, HMGB1, NF- $\kappa$ B p65 and MAPK p38, to increase those of  
580 Nrf2 and to decrease the infiltration of neutrophils and the activity of MPO (Kassim et al., 2012b,  
581 2012c; Ranneh et al., 2019). Additionally, in mice with ear or paw edema, induced by different  
582 chemical substances, such as 2-O-tetradecanoylphorbol 13-acetate (TPA), arachidonic acid,  
583 carrageenan and LPS, and formalin, the extracts of *Mimosa marginata*, Manuka and Kanuka honeys

584 were able to decrease inflammation (TNF- $\alpha$ , IL-6, PGE2, COX-2, NOS), neutrophil infiltration,  
585 intensity of edema and pain, by inhibiting the nuclear translocation and activation of NF- $\kappa$ B and the  
586 cytosolic degradation of I $\kappa$ B $\alpha$  (Fig. 3) (Kassim et al., 2010; Hussein et al., 2012, 2013; Leong et al.,  
587 2012; Borsato et al., 2014; Owoyele et al., 2014).

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

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

604 In addition, honey supplementation can also be a valid ally in ameliorating inflammation in  
605 gastrointestinal and kidney diseases. In this sense, the oral intake of honey has shown to reduce the  
606 levels of the main inflammatory markers and cell infiltration, by decreasing the expression of NF-  
607  $\kappa$ B and inhibiting the activation of NLRP3 inflammasome and the overexpression of TXNIP in  
608 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)-1 $\beta$ ) in sinonasal  
614 tissue as well as in decreasing the synechia 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

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

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

648

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652

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655

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1389 **Figure legends**

1390 **Fig. 1.** The relationship between inflammatory and oxidative stress. Activation of macrophages and  
1391 mitochondrial respiration increase ROS production that leads to tissue oxidation and activates  
1392 cellular signaling pathways MAPKs, PK13, NF- $\kappa$ B and NLRP3 inflammasome. NF- $\kappa$ B upregulates  
1393 proinflammatory cytokines, COX-2, NOS. TNF- $\alpha$ , IL-6, IL-1 stimulate in turn macrophages and  
1394 neutrophils for inflammation process. NADPH oxidase and uncoupled NOS are also responsible for  
1395 ROS production that causes tissue oxidation, necrosis and DNA damage. Necrosis of tissue  
1396 activates, via TRL4 receptor, HMGB1 that in turn activates NF- $\kappa$ B and NLRP3 inflammasome.  
1397 Nrf2 play a significant role for NLRP3 activation by upregulating HO-1 and reducing oxidative  
1398 stress by inhibiting NF- $\kappa$ B signaling and vice versa.

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1400 **Fig. 2.** Schematic representation of the absorption and metabolic processes of the main polyphenols  
1401 present in strawberry and honey.

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1403 **Fig. 3.** Schematic representation of the effects of strawberry and honey on the main molecular  
1404 mechanisms involved in inflammation and antioxidant defense. Strawberry and honey are able to  
1405 modulate the key factors involved in the inflammatory cascade (i.e., NF- $\kappa$ B, Ikk- $\beta$ , AP-1) and in the  
1406 antioxidant defense (i.e., Nrf2 and AMPK).

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**Table 1.** Effect of strawberry on oxidative stress.

Experimental Model	Treatments	Main effects	Ref.
<i>In vitro</i>			
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 <sub>2</sub> O <sub>2</sub>	Strawberry extract: 500 µg/mL for 24 h	-↑ cell viability -↓ ROS -↓ lipid peroxidation -↓ DNA damage -↑ mitochondrial functionality -↑ 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 functionality	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 functionality	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, glutathione-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-Hernandez et 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 functionality	Giampieri et al., 2019
Murine BV-2 microglia stressed with H <sub>2</sub> O <sub>2</sub>	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 <sub>2</sub> O <sub>2</sub>	Digested strawberry extract: 125 µg/mL	-↓citoprotection	Thomas-Valdés et al., 2018
<b><i>In vivo</i></b>			
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 functionality	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 functionality -↑ 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 to 1.5Gy of <sup>56</sup> 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 strawberry extract	-↓ 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 et 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.
<i>In vitro</i>			
Human diploid fibroblasts subjected to $\gamma$ -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 <sub>50</sub> )	-↓ 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 $\mu$ g/ml for 30 min	-↓ oxidative DNA damage	Živković et al., 2018
<i>In vivo</i>			
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	<i>A. cerana</i> 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 <sub>2</sub> -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.
<i>In vitro</i>			
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 <i>H.pylori</i>	Strawberry extract digested <i>in vitro</i> : 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 <i>in vitro</i> aggregation with ADP and arachidonic acid	Strawberry extract: 0.1–1 mg/ml for 15 minutes	-↓IL-1β -↓CD40L -↓RANTES	Alarcòn et al., 2015
<i>In vivo</i>			



36 C57BL/6J mice with diet-induced obesity	Diet supplemented with 2-6 % of strawberry powder for 24 weeks	-↓CRP -↓TNF- $\alpha$ -↓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- $\alpha$ -↓IL-1 $\beta$ -↓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- $\alpha$ -↓IL-1 $\beta$ -↓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 <sup>56</sup> 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- $\alpha$ -↓IL-6 -↓NO -↓MPO	Duarte et al., 2018
Healthy subjects 20–50 years old with a BMI of 30–40 kg/m <sup>2</sup>	Four servings (80 g for each serving)/day for 7 weeks	-↓IL-1 $\beta$ -↓IL-6 -↓TNF- $\alpha$ -↓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-1 $\beta$ -↓IL-6 -↓TNF- $\alpha$ -↓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- $\alpha$ -↓IL-6 -↓IL-1 $\beta$ -↓MMP-3	Schell et al., 2017; Basu et al., 2018

**Table 4.** Effect of honey on inflammation.

Experimental Model	Treatments	Main effects	Ref.
<i>In vitro</i>			
RAW 264.7 macrophages stressed with LPS	Manuka honey 3-8 mg/mL for 24 h	-↓TNF- $\alpha$ -↓IL-1 $\beta$ -↓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- $\gamma$	Gelam honey 0.039-5 mg/mL for 24 h	-↓peroxynitrite	Kassim et al., 2012a
Human keratinocytes exposed to TNF- $\alpha$	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 I $\kappa$ B $\alpha$ -↓IL-1 $\beta$ -↓IL-6 -↓TNF- $\alpha$ -↓COX2 -↓PGE2	Ahmad et al., 2012
Human colorectal adenocarcinoma cell line HT29 stressed with H <sub>2</sub> O <sub>2</sub>	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 <i>H.pylori</i>	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 $\mu$ g/mL for 24 h	-↓p-JNK -↓I $\kappa$ k- $\beta$ -↓TNF- $\alpha$ -↓IL-1 $\beta$ -↑p-Akt	Safi et al., 2016
<i>In vivo</i>			

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 <i>M. marginata</i> 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 IκBα	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 <i>Pseudomonas aeruginosa</i> or <i>Staphylococcus aureus</i>	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- $\beta$ in pancreatic islets -↓IL-1 $\beta$ -↓TNF- $\alpha$ -↓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- $\alpha$ -↓IL-6 -↓IL-1 $\beta$ -↓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-1 $\beta$ -↓TNF- $\alpha$ -↓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- $\alpha$ -↓MCP-1 -↓IL-1 $\beta$ -↓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

64 patients with chronic rhinosinusitis	Thyme honey nasal spray with 35 % w/v honey	-↓MIP-1β -↓inflammatory parameters -↓synechia 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**

