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1 **Berries and oxidative stress markers: an overview of human intervention studies**

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15

16 **Keywords**

17 Berries; Bioactive compounds; Oxidative stress; Dietary intervention studies; Humans

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19 **ABSTRACT**

20 Berries are an excellent source of bioactive compounds such as vitamins, minerals but above all
21 polyphenols with anthocyanins as the most representative compounds. Several *in vitro* and *in vivo*
22 studies documented the beneficial effects of berries and their bioactives in the modulation of
23 numerous cell functions related to oxidative stress and/or antioxidant protection.

24 The following review summarizes published results about the role of berries (either fresh, juice,
25 freeze-dried or dehydrated) on total plasma and serum antioxidant status and on the modulation of
26 biomarkers of oxidative stress in *acute* and *chronic* human intervention trials. The biomarkers
27 considered include DNA, protein and lipid oxidation, and endogenous antioxidant enzymes.

28 Though limited, there is indication that the consumption of berries may reduce oxidative stress by
29 modulating protein and lipid oxidation, and by improving total antioxidant status. In particular,
30 these effects are more evident following medium/long term interventions with respect to
31 postprandial studies. Benefits are observed in healthy subjects as well as in those with
32 cardiovascular risk factors or other diseases. On the contrary, data regarding the effect of berries on
33 DNA damage and endogenous antioxidant enzyme activities are still scarce and inconclusive. In
34 conclusion, much remains to be elucidated before a comprehensive understanding of the effects of
35 berries on the modulation of oxidative stress markers is achieved. Robust clinical evidence
36 supporting the role of berries in counteracting oxidative stress in humans is encouraged.

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44 **INTRODUCTION**

45 In the last decade, polyphenol-rich foods have received increased interest from researchers and the
46 food industry. The main reason for this interest is the recognition of their potential protective effects
47 in human health and disease prevention. Berries are a rich source of polyphenol-bioactives and
48 recent *in vitro* and *in vivo* evidence seems to support their role in the prevention of various diseases
49 associated with oxidative stress.[1-8] Furthermore, they positively affect plasma antioxidant status in
50 humans and they are involved in the modulation of several physiological functions and in the
51 activity of a wide range of endogenous enzymes.[2;9-11] In the present review, we attempt to
52 summarize the main literature on the role of berry consumption on antioxidant status and on the
53 modulation of oxidative stress markers in humans. In particular, we evaluated markers of DNA,
54 protein and lipid damage, and modulation of endogenous antioxidant enzymes following *acute* and
55 *chronic* dietary interventions with berries. Moreover, a short overview on absorption and
56 metabolism of the main berry bioactives and a critical analysis of the studies and their results was
57 included.

58

59 **Berry Fruits, Bioactives and Bioavailability**

60 Among berries, it is necessary to point out that the term "soft fruits" refers to a wide number of
61 berries, mainly belonging to the genera *Vaccinium* and *Rubus*. The most common berries include:
62 highbush blueberry (*Vaccinium corymbosum*), lowbush blueberry (*Vaccinium angustifolium*),
63 bilberry (*Vaccinium myrtillus*), cranberry (*Vaccinium macrocarpon*), blackberry (*Rubus fruticosus*),
64 black raspberry (*Rubus occidentalis*), red raspberry (*Rubus idaeus*), blackcurrant (*Ribes nigrum*),
65 strawberry (*Fragaria ananassa*), lingonberry (*Vaccinium vitis-idaea*), cloudberry (*Rubus*
66 *chamaemorus*), elderberry (*Sambucus nigra L.*), and chokeberry (*Aronia melanocarpa*). Berries can
67 be consumed as fresh fruits as well as ingredients in many processed products including yogurts,
68 purées, juices and jams. Moreover, a raising trend in using berry extracts as ingredients in numerous

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69 dietary supplements has been documented in the last years. In addition, the food industry has
70 pushed toward the use of berries and berry products as functional foods.
71 Most berries contain high levels of phenolic compounds including flavonoids (anthocyanins,
72 flavonols and flavanols), condensed tannins (proanthocyanidins), hydrolyzable tannins
73 (ellagitannins and gallotannins), phenolic acids (hydroxybenzoic and hydroxycinnamic acids,
74 chlorogenic acid), stilbenoids and lignans.[2;12] These compounds are well recognized for their
75 antioxidant activity, which may play a crucial role in the prevention of many chronic diseases.[13]
76 The concentration of phenolic compounds varies according to species, genotype, growing and post-
77 harvesting conditions of berries.[14] The most characteristic group of phenolics in berries is probably
78 the class of anthocyanins (ACNs).[15] More than 500 different ACNs have been described, and six of
79 them (i.e. pelargonidin, cyanidin, delphinidin, petunidin, peonidin, and malvidin) are commonly
80 found in berries. Usually, their content increases during ripening and can reach values up to 4-5
81 g/kg fresh weight (FW) in blackcurrants, black elderberries, blackberries and blueberries[16], and up
82 to 0.6-0.8 g/kg FW in strawberries.[17] ACNs are mainly found in the skin but can also appear in the
83 flesh (e.g. strawberries). It is estimated that the average total intake of ACNs may be approximately
84 200 mg/day[18]; however, they are generally poorly absorbed with less than 1% of the ingested
85 amount reaching the plasma where the concentration ranges between 10 and 50 nmol L^{-1}.[19]
86 Bioavailability differs for the type of berry and the process. Recently, it has been shown that the
87 availability of ACNs from berry juice is lower than that from whole berries.[20] Kuntz and colleagues
88 reported that the absorption of Mv-3-glc after juice intake was lower than that after smoothie
89 ingestion, indicating that malvidin-3-glucoside (Mv-3-glc) from juice was more available (80%
90 relative bioavailability).[20] Del Bo' and co-workers documented that blanching increased the
91 absorption of ACNs in a blueberry purée compared to an unblanched product.[21] Additionally, the
92 bioavailability of ACNs varies markedly depending on the food matrix, including other
93 antioxidants, micronutrients, and macronutrients present in the foods consumed.[22] Nurmi and

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94 colleagues investigated the occurrence of ACNs and phenolic acids (PA) in urine after ingestion of
95 fruit purée with and without oat cereals.[23] They observed a delayed maximum urinary excretion of
96 dietary PA after consumption of purée and cereal compared with consumption of purée alone.[23]
97 Additionally, Cebeci *et al.*[24] documented that whole or skimmed milk did not affect the total
98 phenolic content and the bioavailability of phenolic compounds.
99 After absorption, ACNs are rapidly metabolized to glucuronidated, methylated and sulfated
100 compounds in the liver.[25] Some studies reported that the urinary concentration of glucuronides and
101 methylated glucuronide forms is four to six times higher than the native ACNs.[26,27] In fact,
102 glucuronides and methylated compounds are the predominant forms detected in plasma and urine,
103 while very few studies identified sulphated of the cyanidin-3-glucoside (Cy-3-glc) and Mv-3-
104 glc.[28,29] Most ACNs reach the colon where they are rapidly broken down by the microbiota into
105 phenolic degradation products. These compounds can be absorbed and undergo additional
106 metabolic transformation. These processes may affect the biological activity of the newly
107 constituted compounds.[30]
108 Gallic (GA) and chlorogenic acids (CGA) are the most abundant phenolic compounds in
109 blueberry (up to 2 g/kg FW in particular CGA) and blackberries (about 0.3 g/kg FW), while in
110 strawberries the concentration is low (about 0.09 g/kg FW).[16] GA and conjugates are rapidly
111 absorbed and generally, they reach a maximum concentration between 1 and 2 h in plasma
112 following the consumption of berries.[31] On the contrary, CGA is poorly absorbed; only one-third of
113 ingested amount is absorbed in the small intestine, while the remainder is largely transformed into
114 caffeic acid and/or metabolites.[32]
115 Berries are also an excellent source of flavan-3-ols, a complex subclass of polyphenols
116 without glycosidic residues and with different levels of polymerization including monomers,
117 oligomeric and polymeric proanthocyanidins. These latter compounds can be classified according to
118 their monomeric units (i.e. monomers of epicatechins are named procyanidins) or the position of

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119 carbon-carbon or carbon-oxygen intermolecular bonds. Chokeberries, blueberries and strawberries
120 are a rich source of flavan-3-ols and proanthocyanidins (from 1.5 up to 6.6 g/kg FW), while
121 blackberries and raspberries contain around 0.3 g/kg FW.[16] The bioavailability of these compounds
122 may vary greatly according to their molecular weight and the food matrix. Studies reported that
123 about 8–17% of dietary flavan-3-ols are absorbed in the small intestine, while the unabsorbed
124 fraction reaches the colon where it is transformed into several low molecular weight metabolites
125 (i.e. phenylpropionic, phenylacetic, hippuric, benzoic acids).[16]

126 Hydrolysable tannins are the main group of plant tannins including more than 500
127 compounds composed of sugar polyesters (usually glucose) and phenolic acids. Berries are an
128 important source of ellagiotannins particularly abundant in cloudberry and red raspberry where they
129 account for about 80% of total phenolics (up to 2.6 g/kg FW), and in blackberries, blueberries and
130 strawberries forming 51% of the total compounds (up to 6 g/kg FW).[16] After ingestion, tannins are
131 hydrolyzed to ellagic acid; this compound can be absorbed and metabolized by phase II enzymes
132 into sulfated, glucuronidated and methylated compounds, or by microbiota into urolithins.[16]

133 Berries also contain vitamin C, provitamin A carotenoids, E, and B vitamins that can
134 contribute to antioxidant protection. They are present in honeyberry and blackcurrants in
135 concentration higher than those found in raspberries, gooseberries and strawberries.[2] The level
136 varies according to numerous factors including genetics, environmental and storage conditions.
137 Vitamin C is reported in high amounts in blackcurrants (0.7–2.8 g/kg FW) and strawberries (about
138 0.6 g/kg FW).[1]

139 Berries are also a source of minerals. Some minerals contained in berries such as copper,
140 iron, zinc, manganese and selenium are important cofactors and components of antioxidant enzyme
141 systems (e.g. superoxide dismutase, SOD; glutathione peroxidase, GSH-Px), contributing to
142 antioxidant defense. The major mineral elements found in berries are phosphorus, potassium,
143 calcium, magnesium, iron, manganese, copper, sodium, and aluminum.[2] Blackcurrant, strawberry,

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144 raspberry, blackberry and blueberry contain more calcium (150-350 mg/kg FW), potassium (0.5-3.2
145 g/kg FW) and manganese (12-39 mg/kg FW) compared to other berries.[2;6;17;33]
146
147 **Antioxidant Defense, Oxidative Stress and Biomarkers**

148 Berry bioactive components exert an important role against oxidative insults by acting as
149 scavengers for free radicals. Oxidative stress occurs following an imbalance between the cellular
150 production of oxidant molecules and the availability of antioxidants able to defeat these insults.[34]
151 Reactive oxygen and nitrogen species (ROS/RNS) are the major contributors to the development of
152 oxidative stress. They include superoxide anion ($O_2^{\cdot -}$), hydroxyl radical ($HO^{\cdot}$), lipid radicals (ROO^-
153), nitric oxide (NO), hydrogen peroxide (H_2O_2), peroxynitrite ($ONOO^-$) and hypochlorous acid
154 (HOCl).[35] ROS production is involved in cell damage, necrosis and cell apoptosis due to the
155 oxidation and nitration of cellular proteins, lipids and DNA, that bring loss of cell function.[34] In
156 order to measure oxidative stress conditions, several biomarkers and analytical methods have been
157 developed. The most commonly exploited markers include the evaluation of antioxidant capacity in
158 the bloodstream (serum/plasma), the estimation of antioxidant defense system (enzymes and
159 endogenous compounds), and the evaluation of the levels of oxidative damage to DNA, proteins
160 and lipids. The European Food Safety Authority (EFSA) stated that the protection of tissues, cells,
161 and biomolecules (i.e. DNA, proteins, and lipids) is a beneficial physiological effect for humans;
162 however, the substantiation of antioxidant protection requires target molecules *in vivo* and
163 appropriate methods of assessment. In this regard, the utility and validity of biomarkers for
164 oxidative stress are still under debate and main criticisms reported in the EFSA statements will be
165 mentioned.

166 **-Total Antioxidant Capacity and Defense**

167 Antioxidants exert an important role against free radical damage; thus, measurement of antioxidant
168 levels in biological fluids is used to assess the extent of oxidant exposure, and in turn, oxidative

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169 stress. The evaluation of the antioxidant status represents one of the main approaches used in human
170 studies to evaluate changes of the total antioxidant capacity (TAC) in a target tissue or biological
171 fluids (i.e. plasma/serum) following, for example, a dietary treatment. Numerous methods have
172 been developed and the most common include the total reactive antioxidant potential (TRAP), the
173 trolox-equivalent antioxidant capacity (TEAC), the ferric reducing antioxidant potential (FRAP),
174 the oxygen radical absorbance capacity (ORAC) or the ferrous oxidation-xylenol orange (FOX)
175 assays.[36] They differ from each other in terms of reaction mechanisms, oxidant and target/probe
176 species, reaction condition and expression of the results obtained.[36] Over the years, researchers
177 discussed the validity of these methods emphasizing their numerous limitations. All of them
178 provide an estimate of the antioxidant capacity of plasma/serum without distinguishing the
179 contribution by exogenous molecules of dietary origin (i.e. ascorbic acid, vitamin E, polyphenols)
180 compared to endogenously-derived molecules such as enzymatic components (i.e. SOD, GSH-Px,
181 and catalase, CAT) and small macromolecules (i.e. albumin, bilirubin, ceruloplasmin, ferritin,
182 glutathione).[34] From a clinical perspective, this poses problems for data interpretation. In this
183 regard, EFSA remarked the inappropriateness of the methods used to determine antioxidant
184 capacity in humans and extrapolate possible effects on human health. Since results vary across
185 different TAC assays, these methods should be assessed in parallel with others biomarkers of
186 oxidative damage.[37]

187 SOD, CAT and GSH-Px are the most widely studied enzymes involved in oxidative stress.
188 SOD is involved in the dismutation of superoxide into oxygen and H_2O_2 as part of the antioxidant
189 defense system.[34] GSH-Px is a general name of an enzyme family involved in removal of peroxide
190 in the tissues. They utilize reduced glutathione as a substrate to convert peroxides and
191 hydroperoxide into alcohols, water and oxidized glutathione.[34] Lastly, CAT is a family of enzymes
192 involved in the decomposition of H_2O_2 into water and oxygen. These enzymes work in conjunction

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193 and therefore the measurement of all three together could be useful to determine the antioxidant
194 status.[34]

195 Glutathione S-transferases (GSTs) are a family of enzymes involved in the metabolism of
196 xenobiotics and carcinogens thus they play an important role in the protection against oxidative
197 stress.[34] GSTs bind and conjugate electrophiles to reduced glutathione neutralizing them and
198 protecting the cell from deleterious effects. In addition, some GSTs also have glutathione
199 peroxidase activity.[34]

200 Regarding antioxidant enzymes, EFSA has stated that measurement of enzyme induction alone, is
201 not sufficient as evidence for claims related to the "antioxidant defense system".[37]

202

203 **-Oxidative Damage to DNA**

204 Numerous studies have shown that oxidative DNA damage is associated to a variety of aging-
205 associated degenerative diseases such as cancer and cardiovascular disease (CVD).[38]

206 Genomic damage can be caused by a variety of physical and chemical agents such as ultraviolet and
207 ionizing radiation, xenobiotics and endogenous ROS. The most common types of DNA damage
208 include base loss, base deamination, base alkylation, base dimerization, base oxidation and
209 single/double strand breakage.[39] Nuclear and mitochondrial DNA from tissue and blood
210 lymphocytes can be used to evaluate oxidative damage. ROS formation may lead to oxidized DNA
211 bases, apurinic/apyrimidinic sites or DNA strand breaks. Among all purine and pyridine bases,
212 guanine is the most prone to oxidation and the most commonly oxidized base lesion is the 8-oxo-2'-
213 deoxyguanosine (8-OHdG).[40] 8-oxodG is a biomarker reflecting the balance between oxidative
214 damage and repair rate.[38] It is unstable, mutagenic and it can react with compounds such as
215 peroxynitrite to even more mutagenic lesions. Urinary 8-OHdG has been measured as indicator of
216 oxidative damage.[40] The methods used to estimate 8-OHdG include high performance liquid
217 chromatography-electrochemical detection (HPLC-EC), gas chromatography–mass spectrometry

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218 (GC-MS), LCMS/MS, antibody-based immunoassays, 32P-post-labelling and enzyme-linked
219 immunosorbance assays (ELISA), direct enzymatic detection by using bacterial glycosylases and
220 endonuclease enzymes.[39;41]

221 The single cell gel electrophoresis (comet assay) represents a relatively simple technique
222 that allows the measure of DNA strand breaks at the levels of individual cells. Direct measurements
223 of oxidative damage to DNA could be obtained *in vivo* by using modifications of the comet assay
224 which technique allows the detection of oxidized DNA bases.[37] This assay directly reflects DNA
225 oxidative damage within cells when assessed, for example, in peripheral blood mononuclear cells
226 (PBMCs). The main methods evaluating oxidized DNA bases involve specific enzymes that
227 recognize oxidized bases such as endonuclease III (ENDO III) able to detect oxidized pyrimidine
228 bases, and formamidopyrimidine (FPG) enzyme (FPG-sensitive sites) that acts on oxidized purines.
229 In addition, the comet assay can be used to study DNA *ex vivo* resistance to oxidative stress by
230 incubating the cells with a stressor (e.g. H_2O_2, Fe^{3+}). Measurements of mRNAs of DNA repair
231 enzymes (e.g. oxoguanosine glycosylase 1 and apurinic/apyrimidinic endonuclease 1) has been
232 recently included in several dietary intervention studies, but the results are still inconclusive.[42]
233 Considering the Consensus Statement published by EFSA neither of these measurements alone
234 should be considered sufficiently powerful to assess *in vivo* oxidative damage to DNA and
235 demonstrate antioxidant protection.[37] On the whole, oxidized DNA bases have been recognized as a
236 reliable marker of oxidative damage while other markers may present greater limitations related to
237 the impact of oxidative damage and repair process and to analytical and technical aspects. [37]
238

239 **-Oxidative Damage to Proteins**

240 Proteins represent the major target for biological oxidants as result of their abundance and for their
241 reaction with many species. Reactions can occur with both the side chains and backbone, with the
242 extent of attack at particular sites of the protein. In some cases, damage is limited to specific

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243 residues, whereas with other species (e.g. hydroxyl radicals) damage is widespread and
244 nonspecific.[43]
245 Plasma protein carbonyl content in biological fluids is actually the most generally used marker of
246 protein oxidation. Carbonyl groups (aldehydes and ketones) are produced on protein side chains
247 during the oxidation process.[44] Many assays are available for detection of protein carbonyls. The
248 best approach to determine oxidative damage to proteins can be obtained by means of HPLC-MS.[37]
249 Another marker of protein oxidation is the nitrotyrosine, a product of tyrosine nitration
250 mediated by reactive nitrogen species such as peroxynitrite anion and nitrogen dioxide.
251 Nitrotyrosine in biological fluids and tissues is increasingly being used as an indicator or marker of
252 cell damage, inflammation as well as NO production.[45] The current gold standard technique for the
253 measurement of nitrotyrosine is MS/MS coupled with GC or HPLC as long as identification and
254 separation of such molecule in plasma from other substances is successfully achieved.[46] Other ways
255 of quantifying protein nitration are immunocytochemical and immunohistochemical assays based
256 on either monoclonal or polyclonal anti nitrotyrosine antibodies.[43;47]
257 Regarding the evaluation of oxidative damage to proteins, EFSA has stated that a direct
258 measurement *in vivo* can be obtained by means of HPLC-MS. The use of conventional assays, such
259 as colorimetric or ELISA methods may only be used in combination with at least one direct marker
260 of oxidative damage to proteins *in vivo* if assessed directly in blood or tissue.[37]
261
262 **-Oxidative Damage to Lipids**
263 Lipids are susceptible targets of oxidation because of their molecular structure often abundant in
264 reactive double bounds. Oxidized LDL, lipid hydroperodixe, malondialdehyde (MDA), conjugates
265 dienes, and isoprostanes (F_2-IsoP) are products of lipid peroxidation. Compared to others, F_2-IsoP
266 are chemically stable end-products and for this reason are the most well studied markers.[43]

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267 F_2-IsoPs are a series of prostaglandin F_2a-like compounds produced *in vivo* by non-enzymatic
268 peroxidation of arachidonic acid, esterified in phospholipids and then subsequently hydrolysed to
269 their free acid form by the platelets activating factor acetylhydrolase.[43] IsoPs are released from the
270 cell membrane into circulation by phospholipases, and can be quantified in all human tissues and
271 biological fluids, including plasma, urine, cerebrospinal and broncho-alveolar lavage fluid.[48] Direct
272 measurements of oxidative damage to lipids (i.e. lipid peroxidation) could be obtained *in vivo* by
273 measuring changes in F_2-IsoP in 24-h urine samples (i.e. better matrix than plasma for this
274 measurement).[37] High levels of IsoPs in plasma and urine samples have been shown to correlate
275 with *in vivo* oxidative stress in a number of animal and human studies.[49] IsoPs are elevated in
276 association with risk factors such as hyperhomocysteinemia, hypercholesterolaemia, diabetes
277 mellitus, obesity, cigarette smoking, as well as atherosclerosis.[50]
278 F_2-IsoP levels are also elevated in human atherosclerotic lesions compared with normal vascular
279 tissue, and may participate in the actual pathogenesis of atherosclerosis through effects on
280 vasoconstriction, platelet aggregation, and proliferation of vascular smooth muscle cells.[49-50] F_2-IsoP
281 can be measured using GC/MS, LC/MS, ELISA, and radioimmunoassay in plasma and urine
282 samples[51] even if mass spectrometric techniques still remain the gold standard tecniques for IsoP
283 quantification.[37;50]
284 Oxidative damage to lipids can also be obtained *in vivo* by measuring oxidized low density
285 lipoprotein (LDL) particles. This may be evaluated in blood using immunological methods (i.e.
286 antibodies) with appropriate specificity. Phosphatidylcholine hydroperoxidases measured in blood
287 or tissue by HPLC is also an acceptable marker of lipid peroxidation.[37]
288 Thiobarbituric acid reactive substances, MDA, high density lipoprotein (HDL)-associated
289 paraoxonases, conjugated dienes, breath hydrocarbons, auto-antibodies against LDL particles and
290 *ex vivo* LDL resistance to oxidation have been proposed as markers of lipid damage.[37]

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291 On the whole, EFSA states that the measurement of F_2-IsoP in urine, oxidized-LDL and
292 phosphatidylcholine hydroperoxidases in plasma, represent reliable *in vivo* markers of lipid
293 peroxidation. Other markers could be used in combination, if appropriate techniques are applied for
294 the analysis.[37]

295 **METHODS**
296
297 A search for literature on intervention studies investigating the role of berries in the modulation of
298 antioxidant defense and oxidative stress was carried out. Human *acute* and *chronic* intervention
299 studies involving berries and reporting measurement of oxidative stress markers in cells, plasma,
300 serum, erythrocytes and urine were selected. PUBMED and ScholarGoogle databases were
301 searched to identify papers published later than January 1st 2000.
302 The searches used the following terms and keywords alone and in combination: 'humans', 'berry',
303 'oxidative stress', 'DNA damage', 'lipid damage', 'protein damage' and 'antioxidant capacity'. The
304 selection of markers was carried out taking into consideration those generally reported in
305 intervention trials. Particular attention has been devoted to markers of antioxidant protection and/or
306 oxidative stress for which scientific guidance (reporting biological and methodological critical
307 aspects) has been provided by EFSA[37].
308 Only English-language papers were selected but no other publication data restrictions were applied.
309 Interventions conducted in both healthy and pathological subjects were included in the revision.
310 Fifty-seven scientific papers were obtained from the database searches and from the reference lists
311 of the obtained papers.[52-107] Based on a preliminary review of the abstracts, eight articles were
312 excluded because studies were performed with a mix of fruit and vegetables in which berries were
313 not the main food.[58;63:67-68;71;77;83-84] Moreover, studies were excluded if the control/placebo food
314 included soft fruits, thus the beneficial effect could not be attributed specifically to the berries
315 **(Figure 1)**. No other exclusion criteria was applied (e.g. study design).

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316 Therefore, after exclusions, a total of forty-nine studies investigating effects of soft fruits on
317 markers of oxidative stress was included in the review.[52-57;59-62;64-66;69-70;72-76;78-82;85-108] These papers
318 were published in more than twenty different journals and studies were conducted in sixteen
319 different countries, but mainly USA, Canada, Germany and Italy. The results obtained are reported
320 in **Table 1** and **2** describing the type of food or supplement, the number of intervention days, the
321 number of subjects and their characteristics, the dose/day of test food and the content of its main
322 bioactives, the use of control/placebo food, the outcomes measured and the significant findings.
323

324 **Role of Berries in the Modulation of Biomarkers of Antioxidant Defense and Oxidative Stress**

325 The impact of berry consumption on biomarkers of oxidative stress has been investigated in
326 several *acute* (**Table 1)** and *chronic* (**Table 2)** human intervention studies. Three out of 49 studies
327 performed both the *acute* and *chronic* interventions,[52;61-62] ten were only *acute* studies,[53-57;59-60;64-66]
328 while thirty-six performed *chronic* dietary intervention studies.[69-70;72-76;78-82;85-108] The main berries
329 investigated were bilberries, lingonberries, blueberries, blackcurrants, blackberries, raspberries,
330 cranberries, chokeberries, strawberries, boysenberries, elderberries and whortleberries. Berries were
331 characterized for the content of phenolic compounds (i.e. phenolic acids and ACNs), vitamins and
332 antioxidant activity. Eight studies (one postprandial and seven *chronic* interventions) did not
333 provide information about the composition of berry bioactive compounds.[52;72-73;80-81;88;91;108] The
334 amount of bioactives administered, varied from study to study and it was based on the type of berry,
335 the amount of food administered, and the analytical method used for the characterization of the
336 berries. Thus, comparison among studies and extrapolation of information about dose-response
337 effects appears difficult due to the different characteristics of the tested food and subjects recruited;
338 thus no comparison among studies could be done. Thirty-one studies were performed in healthy
339 subjects,[52-60;62-75;77-79;83-84;87;90-92;97;99-102;105-106;108] six in individuals with metabolic syndrome,[82,85-
340 86,89,95-96] three in subjects with hyperlipidemia,[61;80;104] three studies in subjects with CVD risk

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341 factors,[88;94;98] two studies in people with type 2 diabetes mellitus,[81;93] one study in hypertensive
342 individuals,[106] one study in individuals with fatty liver diseases,[103] and one in subjects with
343 premalignant esophagel condition.[76]
344 In **Table 1** are reported the main results on biomarkers of oxidative stress following the
345 postprandial intake of berries. Of the thirteen studies considered, nine used a single food for the
346 intervention,[53-54;57;59-62;65-66] while five studies tested the effect of a mix of berries.[52,55-56;58;64] Berries
347 were provided mainly in the form of purées, juices or beverages (i.e. obtained by suspending a
348 lyophilized berry product in water), while two studies used the whole fresh food approach.[52;60] The
349 dose of berries varied from 80 to 1000 g for whole berries/purée, and from 240 to 500 mL for the
350 juice/beverage. Regarding the experimental design, most of the studies were placebo-controlled and
351 crossover. Three studies were performed without placebo.[52;60;62]
352 The effect of berries in the modulation of plasma and serum antioxidant status was
353 evaluated in nine studies through TEAC, TRAP and ORAC assay. Eight out of nine studies showed
354 that the intake of a single portion of berries significantly increased serum/plasma antioxidant status
355 compared to the control group as assessed by the methods previously reported.[52-55;57;59-60;64;66] The
356 effect of the modulation of endogenous antioxidant enzymes was investigated only in one study that
357 documented a significant increase in SOD and GSH-Px activity in red blood cells following the
358 consumption of cranberry juice.[66] Thus, no conclusion can be drawn about the role of a single
359 portion of berries in the modulation on such biomarkers.
360 The impact of berry consumption on DNA oxidative damage was evaluated only in two studies. The
361 markers considered were endogenous DNA damage (evaluated as FPG-sensitive sites), DNA *ex*
362 *vivo* resistance to H_2O_2-induced oxidative damage, DNA single strand breaks, and plasma
363 concentration of 8-OHdG. Del Bo' et al.[65] reported that the consumption of a single blueberry purée
364 portion (300 g) was able to decrease oxidatively-induced DNA damage in PBMCs in healthy
365 subjects. On the contrary, no effect was observed for the levels of endogenous DNA damage

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366 implying that long-term supplementation is required to induce modification and protection on
367 purine DNA bases. Mathison et al.[66] documented no effect on plasma levels of 8-OHdG following
368 the consumption of a cranberry leaf extract beverage.

369 The effect of berry consumption on the levels of oxidative protein damage (evaluated as
370 protein carbonyl or total thiol serum groups in the blood) was performed in three studies.[56;62;64] Two
371 of them documented no effect following the consumption of berries in a group of healthy male[62]
372 and of athletic females,[64] while the other one showed a reduction in plasma protein carbonyl levels
373 following the intake of the berry beverage in a group of cyclists.[56] The difference in the results
374 could be attributed to several factors such as the protocols used to perform exercise and to induce an
375 oxidative stress condition to the muscles, the level of training, the different foods tested (blueberry
376 smoothie with banana *versus* a mix of berries *versus* blueberry sorbet), the number and the sex of
377 subjects enrolled (males *versus* females).

378 The effect of berry consumption on lipid oxidation and damage was evaluated in five
379 studies.[52;55-56;61-62] The main biomarkers included diene conjugates, ox-LDL and MDA plasma
380 levels. Three studies reported a significant reduction in lipid damage following the consumption of
381 a single portion of strawberries,[61] blackcurrants,[62] or a mix of berries and fruit juice[55]; while no
382 effect was observed in two studies.[52,56]

383 **Table 2** summarizes the main results related to the effect of *chronic* consumption of berries
384 in the modulation of biomarkers of oxidative stress. A total of thirty-six studies was analyzed.
385 Thirty tested the effect of a single berry[61-62;70-73;75-76;80;82;85-89;91-101;103;105-108], three used a mix of
386 berries[52;79;102] and six were performed with supplements and capsules.[69;74;78;81;90;104] Berries were
387 provided mainly in the form of juices and/or beverages, while in seven studies the whole fresh food
388 was used.[73;80;87;91-92;97;105] The dose of berries varied from 100 g to 500 g for whole berries/purée
389 and from 240 mL to 1000 mL for the juice/beverage. The duration of most studies was 4-6 weeks.
390 Eighteen studies used a parallel experimental design[52;69-70;73;75;78;81-82;88-89;91;93;98;100-101;104;107], seven

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391 a crossover design[61-62;80;94-95;102-103], while fourteen were conducted without a control/placebo group,
392 thus the experimental design was classified as "baseline and post-intervention".[72;74;76;79;85;87;90;92;96-
393 97;99;105-106;108]

394 The evaluation of antioxidant status through TEAC, TRAP and ORAC assays was
395 performed in fifteen out of thirty-six studies.[52;72-75;79;88-89;91-93;97;102;105-106] Twelve studies reported a
396 significant effect following berry consumption,[52;72;74;79;89;91-93;97;102;105-106] while three did not show
397 any effect.[73;75;88] Considering the effect of berries in the modulation of endogenous antioxidant
398 enzymes such as SOD, GST, GSH-Px, only eight studies were conducted.[75;78;87;94;99;102;107-108] Three
399 trials documented a significant increase in enzymes activity following the intervention,[99;102;107]
400 while the others reported no significant findings.[75;78;87;94;108]

401 Twelve studies investigated the effects of berry consumption on the levels of DNA damage,
402 evaluated as DNA strand breaks, endogenous DNA damage (e.g. FPG and EndoIII -sensitive sites),
403 H_2O_2-induced DNA damage and DNA repair capacity, measured by comet assay in PBMCs, and 8-
404 oxodG detected in urine.[70;74-76;79;87;91;94;97;102;105;108] The evaluation of endogenous DNA damage
405 following berry treatment was investigated in three studies.[70;75;94] Only one study showed a
406 significant reduction in the levels of oxidized purines (FPG-sensitive sites) following 6-week wild
407 blueberry intake in subjects with CVD risk factors;[94] one study reported a lack of protective effect
408 on Endo III-sensitive sites,[75] while one study observed a significant increase in the levels of FPG
409 sensitive sites after 3-week blackcurrant intervention in a group of healthy subjects.[70] The authors
410 speculated that the increase of DNA damage in the blackcurrant juice group could be attributed to a
411 possible adverse effect related to the amount of vitamin C introduced (140 mg/day dose) or to a
412 prooxidant effect of polyphenols that chelate iron ions in the presence of vitamin C.[70] However, the
413 authors pointed out that treatment effects did not differ in this respect, and the increase in FPG
414 sensitive sites was rather small.

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415 DNA resistance to oxidative stress was investigated in five dietary intervention studies.[74-75;79;94;105]
416 Three studies documented an improvement in the protection against oxidative damage following 6-
417 week intervention with wild blueberry in subjects with CVD risk factors,[94] 4-week intervention with
418 blueberry/apple juice,[79] and 2-week intervention with strawberries in healthy subjects.[105] On the
419 contrary, no effect was observed after 2-week intervention with cranberry juice,[75] and 4-week
420 consumption of blueberry/apple juice in healthy volunteers.[74] The discrepancy between the two
421 studies performed with blueberry/apple juice by the same authors was attributed to the number of
422 subjects enrolled. In the first pilot trial only eight subjects were recruited and the results
423 documented a large inter-individual variation in the levels of DNA damage. On the other hand, the
424 second trial involved a large group of individuals (168 healthy volunteers) and that was sufficient to
425 demonstrate a significant protection against DNA oxidative insult.

426 Lastly, three studies evaluated the effect of berry intervention on the levels of DNA strand
427 breaks.[87;94;108] All the studies considered did not show a significant effect of berries in the
428 modulation of this marker. No effect was also observed, by Riso and colleagues, for the
429 mechanisms involved in DNA repair capacity following 6-week supplementation with a wild
430 blueberry drink.[94] Probably, a longer-term exposure to diet is required to affect DNA repair
431 mechanisms.

432 The impact of berry intervention on the levels of 8-oxodG was evaluated in six studies.[75-76;87;91;97;102]
433 Four studies showed no effect following the intervention with berries,[75-76;87;102] while only one
434 reported a significant reduction in urinary levels of 8-oxodG after 30 days of strawberry
435 consumption,[97] and a reduction in urinary levels of 5-hydroxymethyl-2'-deoxyuridine (5-OHMU)
436 following 6-week intervention with blueberries.[91] Based on these results, further studies are
437 necessary to elucidate the role of berries in the modulation of 8-oxodG.

438 Six studies investigated the effect of medium/long term berry intervention on the levels of
439 oxidative protein damage evaluated as protein carbonyl, reduced-SH thiols or advanced oxidation

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440 protein products (AOPP) in the blood.[62;78;80;96;103;106] Despite the limited evidence, all the results
441 obtained have shown a protective effect of berries against protein oxidative damage.
442 The effect of berries in the modulation of lipid damage was investigated in twenty-eight
443 studies.[52;61-62;69;72-73;78;80-82;85-93;95-102;104] Nineteen studies documented a beneficial effect on lipid
444 damage,[62;72-73;78;80;82;85-87;89;93;96-102;104] while nine studies did not show any effect.[52;61;69;81;88;90-92;95]
445 The main makers included MDA, ox-LDL, diene conjugates, F_2-IsoP, lipid peroxidation and 4-
446 hydroxynonenal (HNE). MDA was the only marker of lipid damage that revealed a significant
447 reduction following berry intervention. Nine trials investigated the impact of berries on the levels of
448 F_2-IsoP, lipid peroxidation and HNE.[62;73;86;88-89;91;96-97;101] Although limited, the results seem to
449 support the beneficial effects of berry intervention on those markers. On the contrary, results about
450 the effect of berries on ox-LDL are still inconclusive; about half of the studies showed a reduction
451 of ox-LDL levels,[62;72;82;86-87;89] while the other half no effect.[61;69;81;85;95] Regarding diene conjugates,
452 no study documented a significant effect following the intake of berries.[52;80;92] Further studies are
453 necessary to elucidate the role of berries in the modulation of ox-LDL and HNE.
454

455 **MARKERS OF OXIDATIVE STRESS NOT CONSIDERED IN THE REVIEW**

456 Others markers directly or indirectly related to oxidative stress, analyzed in the papers reviewed but
457 not discussed in the report, include markers of endothelial function (i.e. intercellular adhesion
458 molecule 1, vascular cell adhesion molecule 1, flow mediated dilation, reactive hyperemia index)
459 and markers of inflammation (i.e. interleukins, cytokines).
460

461 **CONCLUDING REMARKS AND PERSPECTIVES**

462 In the last years, berries have been the object of several studies for their role in human health and
463 prevention of several degenerative diseases. The following review summed the main evidence,

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464 deriving from acute and chronic human berry intervention studies, on their protective effects against
465 oxidative stress. A total of forty-nine studies was analyzed. Studies were performed in healthy
466 subjects but also in those with CVD risk factors, fatty liver diseases, metabolic syndrome, diabetes,
467 hypertension, hyperlipidemia and cancer. Some studies present limitations due to non
468 randomization and/or lack of control group or control/placebo food, use of non-validated markers,
469 surrogate markers or the use of non appropriate techniques for their evaluation, lack of a complete
470 characterization of food matrix. Moreover, by considering the differences between types of berry
471 and their bioactive composition, the dose, the form (i.e. juice or whole fruit), the application of
472 different methodologies for the evaluation of the biomarkers (direct methods *versus* indirect
473 methods), made it difficult to compare the results obtained among studies. Greater effort in the
474 application of easy, accurate, robust and shared methods is needed in order to promote more rapid
475 and productive comparisons of research findings across different studies.
476 However, though limited, there are indications that the consumption of berries may protect against
477 protein and lipid oxidation, and increase total plasma and serum antioxidant status in humans. Their
478 effects are observed following chronic interventions both in healthy and unhealthy subjects and in
479 those with cardiovascular risk factors, while for acute studies, results they are inconclusive and
480 inconsistent. Furthermore, results on the effects of berries on DNA damage and endogenous
481 antioxidant enzyme activity are still inconsistent both in acute and chronic intervention. In
482 conclusion, much remains to be elucidated before a comprehensive understanding of the beneficial
483 effect of berries on oxidative stress markers in humans. In this regard, the development of robust
484 and well controlled clinical studies is encouraged.
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487

488 **Figure 1: A flow chart highlighting study selection**

489

490 **Legend**

491 *Studies were identified according to the following keywords: ‘humans’, ‘berry’, ‘oxidative stress’,
492 ‘DNA damage’, ‘lipid damage’, ‘protein damage’ and ‘antioxidant capacity’

493

494 **Studies were excluded with the following reasons: 1) use of a mix of fruit and vegetable for the
495 intervention in which berries were not the main food; 2) use of soft fruits for the control/placebo
496 intervention

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Table 1: Role of berries in the modulation of oxidative stress biomarkers: overview of the *acute* human intervention studies

References	Study design	Study population	Berry intervention	Control intervention	Outcome measure	Principal finding
Marniemi *et al.*[52]	Baseline and post intervention	Six healthy men (mean age, 48.7 years; BMI<30 kg/m^2)	240 g of bilberries, lingonberries or blackcurrants (80 g of each) Composition: Not available	None	Antioxidant status measured in the LDL fraction by TRAP assay LDL diene conjugation	Increase in antioxidant status No effect on LDL diene conjugation
Kay and Holub[53]	Single-blind, controlled, crossover intervention	Eight male subjects (mean age, 46.9 ± 1.9 years; mean BMI, 23.8 ± 0.8 kg/m^2)	Wild blueberry: 100 g freeze-dried wild blueberry powder dissolved in 500 mL water with a high-fat meal Composition (100 g): Total phenolics: 2790 mg: ACNs: 1160 mg; Vitamin C: 10 mg; ORAC: 14.7 mmol TE	Control supplement dissolved in 500 mL water with a high-fat meal Composition: Total phenolics (0 mg), ACNs (0 mg), Vitamin C (0 mg)	Serum antioxidant status measured by ORAC assay Total plasma antioxidant status (TAS)	Increase in serum and plasma antioxidant status
Mazza *et al.*[54]	Single-blind, controlled, cross-over intervention	Five male subjects (mean age, 46.9 ± 1.9 years; mean BMI, 23.8 ± 0.8 kg/m^2)	Blueberry: 100g freeze-dried + high fat meal Composition (100 g): Total phenolics: 2790 g; ACNs: 1160 mg; Vitamin C: 10 mg; ORAC: 14.7 mmol TE	Control supplement: 100g (matched the characteristics of blueberry for digestible carbohydrate) + high fat meal Composition (100 g): Total phenolics: 0 g; ACNs: 0 g; Vitamin C: 0 g;	Serum antioxidant capacity measured by TEAC and ORAC	Increase in serum antioxidant capacity

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				ORAC: 500 µmol TE		
Netzel *et al.*[55]	Parallel intervention	Antioxidant-rich juice: six healthy volunteers (3 females / 3 males; range age, 24–31 years; BMI 23.7 kg/m^2) Control group (2 females / 2 males). Subjects characteristic not available.	Antioxidant-rich juice (400 mL) containing 30% white grape, 25% blackcurrant-, 15% elderberry-, 10% sour cherry-, 10% blackberry- and 10% aronia-juice Composition (400 mL): Total phenols : 988 mg GAE; ACNs: 166 mg; Ascorbic acid: 41.2 mg; TEAC: 16.4 mmol TE/L	Tap water (400 mL)	Plasma antioxidant capacity measured by TEAC assay Plasma levels of MDA	Increase in plasma antioxidant capacity Reduction in MDA plasma levels
Morillas-Ruiz *et al.*[56]	Randomized, counterbalanced - double-blind intervention	Antioxidant group: 13 healthy cyclists (mean age, 23±5 years; mean BMI, 23.7±3.9 kg/m^2) Placebo group: 13 healthy cyclists (mean age, 25±7 years; mean BMI, 22.6±4.2 kg/m^2)	Antioxidant beverage (3 mL/kg body weight) containing black grape (81.2 g/L), raspberry (93.0 g/L) and red currant (39.2 g/L) Composition (1L): Total phenolics: 1.41 mg; (ACNs 60%, Hydroxycinnamic acid esters 19%, Ellagic acid 13%, Flavonols: 6%);	Placebo beverage (3 mL/kg) without antioxidants and berries but identical in appearance and taste.	Urine levels of 8-OHdG Plasma levels of protein carbonyl Plasma levels of MDA equivalent (TBARS)	Increase in 8-OHdG urine levels following physical activity in the placebo group Reduction in plasma protein carbonyl levels No effect on MDA plasma levels

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			TAC: 0.41 mmol Trolox			
Netzel *et al.,*[57]	Baseline and post-prandial intervention (each subject acted as own control)	Eight healthy, non-smoking subjects (4 females/ 4 males; range age, 24-34 years; mean BMI, 22.6 ±2.8 kg/m^2)	Elderberry juice: (400 mL) Composition (400 mL): Total phenolics: 2240 mg GAE; Total ACNs: 710 mg; Ascorbic acid: 16 mg; Antioxidant capacity: 9.16 mmol (TEAC assay) and 16.8 mmol (TRAP assay)	Control: 400 mL water	Plasma antioxidant capacity measured by TEAC and TRAP assay	Increase in total plasma antioxidant capacity
Vinson *et al.,*[59]	Baseline and post-prandial intervention	Ten healthy subjects (7 females/ 3 males; range age, 25-38 years; range BMI, 22-33 kg/m^2)	Cranberry juice: (240 mL; 27% cranberry juice + high fructose corn syrup containing 21 g of glucose and 17 g of fructose + 80 mg of vitamin C Composition (240 mL): Catechins: 175 mg CE; Cyanidin: 16 mg; Peonidin: 8 mg; Quercetin: 3 mg	Control juice: same characteristics of high fructose corn syrup + 80 mg of vitamin C	Total plasma antioxidant capacity measured by FRAP assay	Increase in total plasma antioxidant capacity
Tulipani *et al.,*[60]	Baseline and post-prandial intervention	Eight healthy subjects (5females/3 males; mean age, 30±6 years; mean BMI, 24±2 kg/m^2)	Six different strawberry cultivars (1kg) Composition (kg FW, range among 6 cultivars): Vitamin C: 0.28-0.40 g; Folate: 128-	None	Total plasma antioxidant capacity measured by TEAC and FRAP assay	Increase in total plasma antioxidant capacity

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			369 µg; Total phenolics: 1.55-2.62 g GAE; Flavonoids: 0.36-0.71 g; ACNs: 350-560 mg; Antioxidant capacity: 8.34-11.0 mmol TE (FRAP assay) and 11.3-16.1 mmol TE (TEAC assay)			
Burton-Freeman *et al.,*[61]	Randomized, single-blind, placebo-controlled, crossover intervention. Baseline and post-prandial intervention	Twenty-four hyperlipidemic subjects (14 females/10 males; mean age, 50.9 ± 15 years; mean BMI, 29.2 ± 2.3 kg/m^2)	High-fat test meal + strawberry beverage (containing a mixture of cultivated strawberry in freeze-dried form). The beverages contained 10 g/ serving, which was equivalent to 110 g/die of fresh strawberries Composition (10g): Total phenolics: about 338 mg	High-fat test meal + Placebo strawberry-flavored beverage prepared from non-strawberry ingredients to provide, as close as possible, the total energy (calories), macro- and micronutrient content, and fiber content, without bioactive compounds	ox-LDL plasma levels	Reduction of ox-LDL plasma levels
Rosenblat *et al.,*[62]	Cross-over intervention	Six healthy male subjects (range age, 25–30 years; BMI, not available)	Polyphenolic-rich beverages (250 mL/day): 1-acai juice blend (Total polyphenols: 1100 mg GAE); 2 – 100% Concord grape juice (Total	None (baseline values acted as control)	Total thiols (SH) protein group in serum ox-LDL plasma levels and serum lipid peroxidation	No effect on SH protein group levels Reduction in plasma ox-LDL and serum lipid peroxidation following black currant juice

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			polyphenols: 825 mg GAE); 3 – 100% black currant juice (Total polyphenols: 1700 mg GAE); 4– 100% pomegranate juice (Total polyphenols: 1200 mg GAE); 5– red wine (Total polyphenols: 1175 mg GAE)			consumption
McLeay *et al.*,[64]	Randomized, placebo-controlled, crossover intervention	Ten healthy physically active females (mean age, 22 ± 1 years; BMI, not available)	Blueberry beverage: 200 g frozen blueberries, 50 g banana, and 200 mL commercial apple juice Composition (100 mL): Total phenolics: 168mg GAE; ACNs: 96.6mg; Phenolic acids: 26mg; Flavonoids: 10.2 mg; Vitamin C: 45 mg; Vitamin E: 3 mg; ORAC: 5.4 mmol TE	Placebo beverage: 25 g dextrose, 50 g banana, and 200 mL commercial apple juice Composition (100 mL): Total phenolics: 29mg GAE; ACNs (0mg), Phenolic acids: 0.6 mg; Flavonoids: 0mg; Vitamin C: 39.5 mg; Vitamin E: 1mg; ORAC: 5.3 mmol TE	Total plasma antioxidant capacity measured by FRAP assay Plasma protein carbonyls levels	Increase in plasma antioxidant capacity No effect on protein carbonyl plasma levels
Del Bo' *et al.*[65]	Randomized, controlled, crossover intervention	Ten young healthy subjects (mean age, 20.8 ± 1.6 years; mean BMI, 22.5 ± 2.1 kg/m^2)	Blueberry purée (300 g) Composition (300 g): Total phenolics: 727.2 mg GAE; ACNs: 348.3 mg;	Control jelly	DNA SBs (without FPG or H_2O_2), FPG-sensitive sites and H_2O_2-induced DNA damage in PBMCs.	Reduction in H_2O_2-induced DNA damage No effect on DNA SBs and FPG-sensitive sites

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			Vitamin C: 2.4 mg.			
Mathison *et al.*,[66]	Randomized, double-blind, placebo-controlled cross-over intervention	Twelve subjects (6 females/6 males; mean age, 27.5 ± 1.3 years; mean BMI, 23.7 ± 0.9 kg/m^2)	Cranberry leaf extract beverage: 15.2 oz (about 456 mL) Composition (15.2 oz): Vitamin C: nd; Proanthocyanidins: 119 mg; Total phenolics: 111 mg; Total ACNs: nd Low-calorie cranberry juice cocktail: 16 oz (about 480 mL) Composition (16 oz): Vitamin C: 100 mg; Proanthocyanidins: 192 mg; Total phenolics: 338 mg; Total ACNs: 17.4 mg cyanidin-3-galactoside)	Placebo: 15.2 oz (about 456 mL) Composition: Vitamin C: nd; Proanthocyanidins: nd; Total phenolics: 19 mg; Total ACNs: nd	Plasma total antioxidant power Plasma levels of 8-OHdG SOD and GSH-Px activity in red blood cells	No effect of intervention on total plasma antioxidant power and 8-OHdG plasma levels Increase in GSH-Px activity following cranberry leaf extract consumption Increase in SOD activity following low-calorie cranberry juice consumption

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Table 2: Role of berries in the modulation of oxidative stress biomarkers: overview of the *chronic* human intervention studies

References	Duration of intervention	Study design	Study population	Berry intervention	Control intervention	Outcome measures	Principal findings
Marniemi *et al.,*[52]	8 weeks	Parallel intervention	Sixty men, 60 years old, BMI<30 kg/m^2	Berry group: 100 g/day of bilberries, lingonberries or blackcurrants in any order Supplement group: supplement of 100 mg/day of Tocopherol, and 500 mg/day of Ascorbic acid	Control group: 500 mg calcium gluconate	Antioxidant capacity measured in LDL fraction by TRAP assay Total and LDL serum diene conjugation	No effect on LDL antioxidant capacity following berries Increase in LDL antioxidant capacity following supplementation No effect on total and LDL serum diene conjugation
Murkovic *et al.,*[69]	3 weeks	Randomized, placebo-controlled parallel intervention	Fourteen healthy subjects (7 females/7 males) Elderberry group: 7 subjects (subjects characteristics not available) Placebo group: 7 subjects (subjects characteristics not available)	Elderberry group: capsules (400mg spray-dried powder containing 10% ACNs; equivalent to 5 mL elderberry juice) Composition: ACNs: 100 mg	Placebo group: capsules (400mg spray-dried powder ACNs free) Composition: No ACNs	Ox-LDL plasma levels	No effect on ox-LDL plasma levels
Møller *et al.,*[70]	3 weeks	Randomized, controlled parallel intervention	Eighteen (11 females / 7 males) healthy subjects for blackcurrant juice (range age, 20-45 yeas; range BMI, 19.6–29.1	Blackcurrant drink (475 to 1000 mL/day according to body weight) ACNs: 397 mg/day; Vitamin C: 140	Control drink (475 to 1000 mL/day according to body weight) No ACNs and vitamin C	SB, Endo III and FPG- sensitive sites in MNBCs	Increase in FPG-sensitive sites. No effect on DNA SB and Endo III sensitive sites in MNBCs

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			kg/m^2) Twenty (14 females / 6 males) healthy subjects for ACN drink (range age, 21-52 years; range BMI, 19.1-27.2 kg/m^2) Nineteen (12 females / 7 males) healthy subjects for control intervention (range age, 19-46 years; range BMI, 19.1-28.1 kg/m^2)	mg/day ACN drink: 475 to 1000 mL/day according to body weight) ACNs: 365 mg/day			
Ruel *et al.,*[72]	2 weeks	Baseline and post-intervention	Twenty-one healthy men (mean age, 38 ±8 years; mean BMI, 26.9 ± 3.8 kg/m^2)	Cranberry juice (7 mL/kg body weight per day) Composition: Not available	None	Plasma antioxidant capacity measured by metmyoglobin assay ox-LDL plasma levels	Increase in total plasma antioxidant capacity Reduction in ox-LDL plasma levels
McAnulty *et al.,*[73]	3 weeks	Randomized, controlled, parallel intervention	Twenty healthy smoker subjects Blueberry group: (mean age, 25.9 ± 3.3 years; mean BMI, 29.7 ± 2.9 kg/m^2) Control group: (29.4 ± 4.2 years; mean BMI, 29.0 ±3.2 kg/m^2)	Fresh blueberry (250g/day) Composition: Not available	Diet blueberry-free	Total plasma antioxidant capacity measured by FRAP assay Plasma F_2-isoprostanes and LH levels	No effect on total plasma antioxidant capacity Reduction in LH plasma levels No effect on F_2-isoprostane plasma levels
Wilms *et al.,*[74]	4 weeks	Baseline and post-intervention	Eight healthy non-smokers	Blueberry juice and apple juice (50:50	None	Total Plasma antioxidant capacity	Increase in total plasma antioxidant

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			female subjects (range age 21-29 years; BMI, not available)	v/v; 1L /day) Composition (1 L): Quercetin: 18 mg		measured by TEAC assay H_2O_2-induced DNA damage in PBMCs	capacity No effect on the levels of DNA damage
Duthie *et al.,*[75]	2 weeks	Randomized, controlled, parallel intervention	Twenty healthy females (range age, 18–40 years) Cranberry group (11 subjects; mean age, 27.3±6.5 years; BMI, not available) Placebo group (9 subjects; mean age, 28.3 ± 7.5 years; BMI, not available)	Cranberry juice (750 mL/day) Composition (750 mL): Vitamin C: 672.75 mg; Total phenols: 852 mg GAE; Catechins: 21.8 mg; ACNs: 2.1 mg as malvidin-3-glycoside equivalents; Antioxidant capacity: 10.5 mmol FeII (FRAP assay)	Placebo drink (750 mL/day) prepared with natural mineral water, strawberry flavor, sucrose (9 g/100 mL) Composition (750 mL): Placebo drink: Vitamin C (1.38 mg), Total phenols (6.72 mg GAE) ACNs: nd; TAC: 0.045 mmol FeII (FRAP assay)	Total plasma antioxidant capacity measured by FRAP and ESR assay (Fremy's radical reduction) GSH-Px, CAT, and SOD activity in erythrocytes DNA SB, H_2O_2-induced DNA damage, Endo III sensitive bases in lymphocytes. 8-OHdG in urine.	No effect on total plasma antioxidant capacity No effect on erythrocytes GSH-Px, CAT and SOD activity No effect on SB, Endo III sensitive sites or H_2O_2-induced DNA damage in lymphocytes. No effect on the levels of 8-OHdG in urine
Kresty *et al.,*[76]	6 months	Baseline and post-intervention	Twenty males and females (range age, 48–68 years, range BMI, 24.84–40.97 kg/m^2) with Barrett's esophagus (premalignant Esophageal condition)	Black raspberries drink (170 mL/day) prepared suspending 32 g for females and 45 g for males of lyophilized black raspberries in 170 mL of water Composition (100 g): Total phenolics: 5938 mg; Ellagic acid: 185 mg;	None	Urine levels of 8-OHdG	No effect on 8-OHdG urine levels (only 10 subjects completed the study)

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				Vitamin C: 2 mg; ORAC: 60.1 mmol TE For men: Total phenolics: 2672.1 mg; Ellagic acid: 83.25 mg; Vitamin C: 0.9 mg; ORAC: 60.1 mmol TE For women: Total phenolics: 1900.16 mg; Ellagic acid: 59.2 mg; Vitamin C: 0.64 mg; ORAC: 60.1 mmol TE			
Valentová *et al.*,[78]	8 weeks	Randomized, placebo-controlled, parallel intervention	Dried cranberry group I: 20 healthy young women (mean age 21.4± 2.0 years; mean BMI, 21.2 ±1.5 kg/m^2) Dried cranberry group II: 22 healthy young women (mean age, 21.7±2.0 years; mean BMI, 20.5±1.8 kg/m^2) Placebo group: 23 healthy young women (mean age,	Dried cranberry group I: 400 mg (two capsules once)/day Composition (400 mg): Total polyphenolic content: 12 mg; Quercetin: 1.2 mg; ACNs: 1.76 mg Dried cranberry group II: 1200 mg (two capsules three times)/day Composition (1200 mg): Total polyphenolic	Placebo group: (two capsules/day)	Serum levels of oxidation protein Products (AOPP), SH group MDA serum and erythrocyte levels SOD and GSH-Px erythrocyte activity	Reduction in AOPP and SH group levels following cranberry (1200 mg/die) intervention. Reduction in MDA serum levels but increase in erythrocytes following cranberry (1200 mg/die) intervention. No effect on SOD and GSH-Px activity.

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			21.7±2.0 years; mean BMI, 21.2±2.1kg/m^2)	content:36 mg; Quercetin: 3.6 mg; ACNs: 5.28 mg			
Wilms *et al.,*[79]	4 weeks	Baseline and post-intervention	One hundred sixty-eight healthy nonsmokers subjects (114 females/54 males; range age, 18-45 years; BMI, not available)	Blueberry/apple juice 50:50 (1 L/day) Composition (1L): Quercetin: 97 mg; Ascorbic acid: 16 mg	None	Total plasma antioxidant capacity measured by TEAC assay H_2O_2-induced DNA damage in PBMCs	Increase in plasma total antioxidant status Increase protection against *ex vivo* H_2O_2-oxidative DNA damage
Jenkins *et al.,*[80]	30 days	Randomized, controlled, cross-over intervention	Twenty-eight hyperlipidemic subjects (range age, 38-75 years; range BMI, 19.8-32.3 kg/m^2)	Strawberries (454 g/day) Composition: Not available	Oat bran bread (65 g/day) as control diet	Serum levels of reduced thiol (−SH) groups as a measure of protein oxidation Plasma levels of MDA equivalent (TBARS) and conjugated dienes	Reduction in oxidative protein damage following both interventions Reduction in MDA plasma levels No effect on plasma levels of conjugated dienes
Lee *et al.,*[81]	12 weeks	Randomized, placebo-controlled, double-blind parallel intervention	Cranberry group: Fifteen subjects with type 2 diabetes (6 females/9 males; mean age, 65±2 years; mean BMI, 26.2±0.7 kg/m^2) Control group: Fifteen subjects with type 2 diabetes (8 females /7 males; mean age, 66±2 years; mean BMI,	Cranberry extracts (one capsule 500mg/day) Composition: Not available	Placebo capsules (500mg/day)	ox-LDL plasma levels	No effect on ox-LDL plasma levels

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			25.9±1.0 kg/m^2)				
Ruel *et al.,*[82]	12 weeks	Parallel intervention	Thirty-one men (mean age, 51 ±10 years; mean BMI, 27.8 ± 3.2 kg/m^2) with (n=9) and without (n=21) metabolic syndrome	Low-calorie cranberry juice concentrate: 125 mL/day (first 4 weeks), 250 ml/die (second 4 weeks) and 500 ml/die (third 4 weeks) Composition (125 mL): Total phenolics: 100 mg; ACNs: 5.2 mg; Proanthocyanidins: 74 mg; Ascorbic acid: 32 mg	Low-calorie placebo juice (cranberry flavored): 500mL/day during run-in period (4 weeks before intervention) Composition (125 mL): Total phenolics: 39 mg; ACNs: nd Proanthocyanidins: nd; Ascorbic acid: 32 mg/125mL	ox-LDL plasma levels	Reduction of ox-LDL plasma levels
Basu *et al.,*[85]	4 weeks	Baseline and post-intervention	Sixteen female (range age, 39-71 years; mean BMI, 38.6 ± 2.3 kg/m^2) with metabolic syndrome	Two cups of strawberry drink per day (each cup containing 25 g of freeze-dried strawberry powder, one cup of water, one teaspoon of artificial sweetener, and one teaspoon vanilla essence). Composition (25 g): Vitamin C: 109 mg; Total phenolics: 2006 mg GAE; ACNs: 154 mg CGE; Ellagic acid: 41 mg	None	MDA, HNE and ox-LDL plasma levels	Reduction in lipid peroxidation No effect on ox-LDL plasma levels
Basu *et al.,*[86]	8 weeks	Single-blinded	Forty-eight	Two cups of	Two cups of water	MDA, HNE and ox-	Reduction in MDA,

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		controlled parallel intervention	subjects with metabolic syndrome Blueberry group (23 females/2 males; mean age, 51.5 ± 3.0 years; mean BMI, 38.1 ± 1.5 kg/m^2) Control group (21 females/2 males; mean age, 48.0 ± 3.3 years; mean BMI, 37.5 ± 3.0 kg/m^2)	blueberry drink/die (50 g of freeze-dried blueberry powder and vanilla essence). Composition (50 g): ACNs:742 mg; Phenolic compounds: 1624 mg; ORAC: 17.8 mmol TE		LDL plasma levels	HNE and ox-LDL plasma levels
Burton-Freeman *et al.,*[61]	6 weeks	Randomized, single-blind, placebo-controlled, crossover intervention	Twenty-four hyperlipidemic subjects (14 females/10 males; mean age, 50.9 ± 15 years; mean BMI, 29.2 ± 2.3 kg/m^2)	Strawberry drink containing a mixture of cultivated strawberry in freeze-dried form. The beverages contained 10 g/ serving (equivalent to 110 g/day of fresh strawberries). At the study day, (after 6 weeks intervention) subjects consumed a high fat meal Composition (10 g): Total phenolics: about 338 mg	Placebo (strawberry-flavored) drink prepared from non-strawberry ingredients to provide, as close as possible, the total energy (calories), macro- and micronutrient content, and fiber content, without bioactive compounds. At the study day (after 6 weeks intervention), subjects consumed a high fat meal	ox-LDL plasma levels	No significant effect on ox-LDL plasma levels
Henning *et al.,*[87]	3 weeks	Baseline and	Twenty-one	Strawberries	None	Serum GST activity	No effect on serum

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		post-intervention	healthy female subjects (mean age, 29.0 ± 6.3 years; mean BMI, 22.2 ± 3.5 kg/m^2)	(250g/day) Composition (250 g): Pelargonidin-3-glucoside: 164.5 mg; Ellagic acid: 3.7 mg		DNA SBs, 8-OHdG and dG in DNA of mononuclear lymphocytes ox-LDL plasma levels	GST activity No effect on DNA SBs, 8-OHdG and dG levels Reduction in ox-LDL plasma levels
Karlsen *et al.,*[88]	4 weeks	Randomized, controlled, parallel intervention	Berry group: Thirty-one subjects (10 females / 21 males; range age, 34–68 years; range BMI, 19.9-31.7 kg/m^2) with elevated levels of at least one risk factor for CVD Control group: Thirty-one subjects (7 females/25 males; range age, 30–68 years; range BMI, 17.8-31.5 kg/m^2) with elevated levels of at least one risk factor for CVD	Bilberry juice: 330 mL/day diluted to 1 L using tap water) Composition: Not available	Control group: Water (1 L/ day)	Total plasma antioxidant capacity measured by FRAP, TRAP and ORAC assay Plasma lipid peroxidation measured by Diacrons reactive oxygen metabolites	No effect on total plasma antioxidant capacity No effect on markers of lipid peroxidation.
Rosenblat *et al.,*[62]	1 week	Cross-over intervention	Six healthy male subjects (range age, 25–30 years; BMI, not available)	Polyphenolic-rich beverages (250 mL/day): 1-acai juice blend (Total	None (baseline values acted as control)	Serum levels of total thiols group	Increase in total thiols group following black currant and pomegranate juice consumption

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				polyphenols: 1100 mg GAE); 2 – 100% Concord grape juice (Total polyphenols: 825 mg GAE); 3 – 100% black currant juice (Total polyphenols: 1700 mg GAE); 4– 100% pomegranate juice (Total polyphenols: 1200 mg GAE); 5– red wine (Total polyphenols: 1175 mg GAE)		ox-LDL plasma levels and serum lipid peroxidation	Reduction in plasma ox-LDL and serum lipid peroxidation following pomegranate and black currant juice consumption
Basu *et al.,*[89]	8 weeks	Randomized, double-blind, placebo-controlled, parallel intervention	Thirty-one females (mean age, 52.0 ± 8.0 years; mean BMI, 40.0 ± 7.7 kg/m^2) with metabolic syndrome	Low energy cranberry juice (480 mL/day) Composition (480 mL): Vitamin C: 120 mg; Total phenolics: 458 mg; Proanthocyanidins: 119.0 mg; ACNs: 24.8 mg	Placebo (480 mL/day) was identical to cranberry juice but free of phenolic compounds	Plasma antioxidant capacity measured by metmyoglobin assay Plasma levels of oxidized LDL; serum levels of MDA and HNE	Increase in total antioxidant status Reduction in plasma oxidized-LDL levels, and serum MDA and HNE levels
Lee *et al.,*[90]	4 weeks	Baseline and post-intervention	Fifteen healthy subjects (mean age, 24.3 ± 1.9 years; mean BMI, 22.1 ± 1.7 kg/m^2)	Supplements containing 30 g of freeze-dried raspberry Composition (30 g): Vitamin E: 2.88 mg; Phenols: 315 mg; Vitamin A: 0.39 mg	None	Plasma levels of MDA equivalent (TBARS)	No effect on MDA plasma levels
McAnulty *et al.,*[91]	6 weeks +	Randomized,	Blueberry group:	Fresh blueberry	No blueberry	Total plasma	Increase in total

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	postprandial and exercise (2.5-h treadmill run)	controlled, parallel intervention	Thirteen sportive subjects (mean age, 31.1 ± 12.6 years; BMI, not available) Control group: Twelve sportive subjects (mean age, 33.4 ± 16.0 years; BMI, not available)	(250 g/day) + 375 g 1h before exercise Composition: Not available		antioxidant capacity measured by FRAP assay 8-OHdG and 5-OHMU in urine Plasma F_2-isoprostanes levels	plasma antioxidant capacity in blueberry and control group following exercise. Reduction in 5-OHMU urine levels following post-exercise in the blueberry group. No effect on the levels of 8-OHdG in urine Increase in plasma isoprostanes levels following post-exercise in the control group with respect to blueberry group
Tulipani *et al.,*[92]	16 days	Baseline and post-intervention	Twelve healthy individuals (7 females/ 5 males; mean age, 34 ± 8 years; mean BMI, 22.2 ±2.4 kg/m^2)	Fresh strawberry (500g/day) Composition (500 g): Vitamin C: 0.18 g; Total folate: 119.4 µg; Total phenols: 1.9 g GAE; Total flavonoids: 0.4 g; Total ACNs: 150 mg; Antioxidant capacity: 6.1 mmol TE (FRAP assay) and 20.3 mmol TE (TEAC assay)	None	Total plasma antioxidant capacity measured by TEAC and FRAP assay Plasma levels of conjugated dienes	Increase in plasma antioxidant capacity, measured by FRAP but not TEAC assay No effect on plasma levels of conjugated dienes
Moazen *et al.,*[93]	6 weeks	Randomized double-blind	Thirty-six subjects (23	Freeze-dried strawberry (50g,	Placebo powder (40g/day),	Total serum antioxidant status	Increase in total serum antioxidant status

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		controlled parallel intervention	females / 13 males) with type 2 diabetes (mean age, 51.57 ± 10 years; mean BMI, 27.90 ± 3.7 kg/m^2) Freeze-dried strawberry group: 19 diabetic subjects (mean age, 51.88 ± 8.26 years; mean BMI, 27.32 ± 3.26 kg/m^2) Placebo group: 17 diabetic subjects (mean age, 51.17 ± 13.88 years; mean BMI, 28.70 ± 4.24 kg/m^2)	equivalent to 500g fresh strawberries)/day Composition (50 g): Total phenolics: 2006 mg GAE; total ACNs: 154mg CGE; Vitamin C: 109mg	identical to strawberry powder in appearance, containing 4g of pectin, 12g of lactose, 4g of instant sugar-free drink powder with strawberry flavor	measured by ORAC assay Serum levels of MDA equivalent (TBARS)	 Reduction in MDA serum levels
Riso *et al.*,[94]	6 weeks	Randomized, controlled, crossover intervention	Twenty subjects with cardiovascular risk factors (mean age, 47.8 ± 9.7 years; mean BMI, 24.8 ± 2.6 kg/m^2)	Wild blueberry drink (250 mL/day natural mineral water, 25g wild blueberry powder) Composition (250 mL): ACNs: 375 mg; Vitamin C: 4.2 mg	Placebo drink: natural mineral water (250 mL/day) with blueberry flavor, colorants, sugars	GST, SOD and GSH-Px activity in red blood cells DNA SBs (without FPG or H_2O_2), FPG-sensitive sites and H_2O_2-induced DNA damage, DNA repair capacity in PBMCs	No significant effect on GST, SOD and GSH-Px activity Reduction in FPG-sensitive sites and H_2O_2-induced DNA damage. No effect on DNA SBs and DNA repair capacity
Ruel *et al.*,[95]	4 weeks	Randomized, placebo-controlled	Thirty-five men (mean age, 45 ± 10 years; mean	Low-calorie cranberry juice concentrate (27%	Placebo juice (500 mL/day) of water + vitamin C. Taste,	ox-LDL plasma levels	No effect on ox-LDL plasma levels

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		double-blind crossover intervention	BMI, 28.3 ± 2.4 kg/m^2) with (n= 13) and without (n=22) metabolic syndrome	juice; 500 mL/day) Composition (500 mL): Total polyphenols: 400 mg; ACNs: 20.8 mg; Proanthocyanidins: 296 mg; Ascorbic acid: 128 mg	color and texture similar to cranberry juice		
Simão *et al.,*[96]	60 days	Baseline and post-intervention	Cranberry group: 20 subjects with metabolic syndrome (14 females /6 males; range age, 42.0–53.0 years; range BMI, 26.3–38.4 kg/m^2) Control group: 36 subjects with metabolic syndrome (28 females / 8 males; range age, 44.8–56.3 years; range BMI, 31.32–36.9 kg/m^2)	Cranberry juice (700 mL/day) Composition (700 mL): Vitamin C: 210 mg; Proanthocyanidins: 231 mg; Total phenolics: 364 mg; Folic acid: 0.42 mg; TEAC:128.6 mmol TE	None	Plasma levels of AOPP Plasma levels of lipid hydroperoxides	Reduction in AOPP plasma levels Reduction in lipoperoxidation
Alvarez-Suarez *et al.,*[97]	30 days	Baseline and post-intervention	Twenty-three healthy volunteers (12 females/ 11 males; mean age, 27 ± 3.2 years; mean BMI, 21.74 ± 2.5 kg/m^2)	Fresh strawberry: (500g/day) Composition (500 g): Vitamin C: 170 mg; ACNs: 307.59 mg; Total phenolics: 1130 mg; Total	None	Total plasma antioxidant capacity measured by FRAP and ORAC assay 8-OHdG in urine	Increase in plasma total antioxidant capacity Reduction in 8-OHdG urine levels

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				flavonoids: 470 mg; Antioxidant capacity: 5.53 µmol TE/ L (FRAP assay) and 24.8 µmol TE/L (ORAC assay)		Plasma MDA and urinary isoprostanes levels	Reduction in MDA plasma levels and urinary isoprostanes
Basu *et al.*,[98]	3 months	Randomized, controlled, parallel intervention	Sixty volunteers with CVD risk factors LD-FDS: 15 subjects (14 females / 1 male; mean age, 50 ± 10 years; mean BMI, 34.5 ± 4.4 kg/m^2) HD-FDS: 15 subjects (13 females / 2 males; mean age, 49 ± 11 years; mean BMI, 38.0 ± 7.1 kg/m^2) LD-C: 15 subjects (14 females / 1 male; mean age, 48 ± 10 years; mean BMI, 37.0 ± 4.4 kg/m^2) HD-C: 15 subjects (14 females / 2 male; mean age, 48 ± 10 years; mean BMI, 35.0 ± 5.2 kg/m^2)	Low dose freeze-dried strawberries (LD-FDS): 25 g of freeze-dried powder reconstituted in 2 cups (474 mL/day) of water daily (corresponding to 250 g of fresh strawberries); Composition (25 g): Vitamin C: 55 mg; Total phenolics: 1001 mg GAE; ACNs: 78 mg; Ellagic acid: 106 mg High dose freeze-dried strawberries (HD-FDS): 50 g of freeze-dried powder reconstitute in 2 cups (474 mL/die) of water (corresponding to 500 g of fresh strawberries) Composition (50 g): Vitamin C: 109 mg; Total phenolics:	Low-dose calorie- and fiber-matched control (LD-C): 4 g of fiber and 5 teaspoons (20 g) of cane sugar, blended in 2 cups (474 mL/day) of water. Red food color and artificial strawberry-flavored was added to mimic the color and flavor of the FDS beverages High-dose calorie- and fiber-matched control (HD-C): 8 g of fiber and 9 teaspoons (36 g) of cane sugar, blended in 2 cups (474 mL/day) of water. Red food color and artificial strawberry-flavored was added to mimic the color and flavor of the FDS beverages	MDA serum levels	Reduction in MDA serum levels

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				2005 mg GAE; ACNs: 155 mg; Ellagic acid: 220 mg			
Kardum *et al.*,[99]	3 months	Baseline and post-intervention	Twenty-five healthy women subjects (mean age, 35.2 ± 7.7 years; BMI, not available)	Polyphenol-rich chokeberry juice (100 mL/day) Composition (100 g): Total phenolics: 386 mg GAE; Total proanthocyanidins: 442 mg CE; Total ACNs: 153.9 mg; Chlorogenic acids: 60 mg; Total quercetin glycosides: 18 mg	None	SOD and GSH-Px activities in red blood cells Plasma levels of MDA equivalent (TBARS)	Increase in SOD and GSH-Px activities Reduction in MDA serum levels
Kaume *et al.*,[100]	9 months	Randomized, controlled, parallel intervention	Forty-five postmenopausal smokers and twenty postmenopausal nonsmokers NS group (non-smokers group): 20 postmenopausal (mean age, 58.0 ± 0.9 years; mean BMI, 23.7 ± 1.5 kg/m^2) SC group (control group): 21 postmenopausal smokers (mean age, 54.4 ± 0.9	S-BB group: 45 g/day freeze-dried blackberry Composition (45 g): Total ACNs: 284.09 mg; Total flavanols: 33.48 mg; Total ellagiotannins: 111.96 mg; Chlorogenic acid: nd S-BL group: 45 g/ day freeze-dried blueberry Composition (45 g): Total ACNs: 652.14 mg; Total flavanols:	Control group was only directed to maintain their usual diet	Serum levels of MDA equivalent (TBARS)	Reduction in serum levels of MDA in the S-BB and S-BL groups

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			years; mean BMI, 27.8 ± 1.4 kg/m^2) S-BB group (blackberries group) : 8 postmenopausal smokers (mean age, 54.3 ± 1.6 years; mean BMI, 25.2 ± 2.5 kg/m^2) S-BL group (blueberry group): 16 postmenopausal smokers (mean age, 54.2 ± 11 years; mean BMI, 29.3 ± 1.7 kg/m^2)	35.92 mg; Total ellagiotannins: nd; Chlorogenic acid: 72.93 mg			
Khan *et al.,*[101]	6 weeks	Randomized, double- blind, placebo-controlled, parallel intervention	Low blackcurrant group: Twenty-two healthy subjects (7 females / 15 males; mean age, 55 ± 10 years; mean BMI, 28.4 ± 5.4 kg/m^2) High blackcurrant group: Twenty-one healthy subjects (8 females /13 males; mean age, 51 ± 11 years; mean BMI, 29.2 ± 6.9 kg/m^2)	Low (6.4% juice) blackcurrant drink (250 mL/4 times per day) Composition (250 mL): Vitamin C: 2.75 mg; Total phenolics: 68.25 mg; ACNs: 10 mg High (20% juice) blackcurrant drink (250mL/4 times day) Composition (250	Placebo drink (flavored water, 250 mL/ 4 times per day)	Isoprostanes plasma levels	Reduction in isoprostanes plasma levels only following intervention with high blackcurrant drink

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			Placebo group: Twenty-one healthy subjects (6 females/ 15 males; mean age, 51 ± 8 years; mean BMI, 28.9 ± 6.5 kg/m^2)	mL): Vitamin C: 25.5 mg; Total phenolics: 203.75 mg; ACNs: 35.75 mg			
Kuntz *et al.,*[102]	2 weeks	Randomized, double-blind, placebo-controlled, cross-over intervention	Thirty healthy female subjects (range age, 23-27 years; range BMI, 18.2-27.9 kg/m^2)	ACN-rich juice: 80% red grape and 20% bilberry juice (0.33 L/day) Composition (0.33 L): Ascorbic acid: 33.66 mg; Total phenolics: 1064.91 mg CE; ACNs: 277.2 mg ACN-rich smoothie: 80% red grape purée and 20% bilberry purée (0.33 L/die) Composition (0.33L): Ascorbic acid: 38.94 mg; Total phenolics: 1133.55 mg CE; ACNs: 324.39 mg	Placebo juice: 100% grape juice 0.33 L/day Composition (0.33 L): Ascorbic acid: 7.26 mg; Total phenolics: 59.07 mg CE; ACNS: 2.96 mg	Plasma antioxidant capacity measured by TEAC assay Plasma SOD, GSH-Px, CAT and erythrocyte SOD activities 8-OH-dG urine levels Plasma and urine levels of MDA equivalent (TBARS)	Increase in plasma antioxidant capacity Increase in plasma SOD and CAT activity No effect on plasma GSH-Px and erythrocyte SOD activity No effect on 8-OH-dG urine levels Reduction in plasma and urinary MDA levels
Guo *et al.,*[103]	4 weeks	Randomized, placebo-controlled, double-blind, crossover intervention	Forty-four subjects (males and females; range age, 18–25 years; BMI ≥ 23.1 kg/m^2), with fatty	Bayberry juice (500 mL/day) Composition (500 mL): Total polyphenols: 1351 mg GAE;	Placebo juice (500 mL/day) Composition (500 mL): taste and color similar to bayberry juice.	Protein carbonyl groups plasma levels	Reduction in protein plasma carbonyl groups following bayberry juice

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			liver diseases	ACNs: 417.5 mg; Ascorbic acid: 493 mg	Ascorbic acid: 500 mg		
Soltani *et al.*,[104]	4 weeks	Randomized, double-blind, placebo-controlled, parallel intervention	Whortleberry group: twenty-five hyperlipidemic subjects (15 females / 10 males; mean age, 48.08±16.39 years, mean BMI, 25.40±1.75 kg/m^2) Placebo group: twenty-five hyperlipidemic subjects (15 females / 10 males; mean age, 46.36±16.59 years, mean BMI, 25.21±2.01 kg/m^2)	Whortleberry capsules (2 capsules/day). Composition (2 capsules): ACNs: 45 mg	Placebo capsules (2 capsules/day): shape, color, and size similar to whortleberry capsules	MDA serum levels	Reduction in MDA plasma levels
Tulipani *et al.*,[105]	2 weeks	Baseline and post-intervention	Eighteen healthy subjects (10 females /8 males; mean age, 35 ± 10 years; mean BMI, 23 ± 3 kg/m^2)	Fresh strawberry (500g/day) Composition (500 g): Vitamin C: 220 mg; Total folate: 144.6 µg; Total phenols: 700 mg; Total flavonoids: 100 mg; Total ACNs: 318.81 mg; Antioxidant capacity: 6.6 mmol	None	Total plasma antioxidant capacity measured by TEAC and FRAP assay H_2O_2-induced DNA damage in PBMCs	No effect on total plasma antioxidant capacity Reduction in DNA damage measured as comet area, comet length and tail length, while increase in the percentage of DNA in tail

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				TE (FRAP assay) and 10.7 mmol TE (TEAC assay)			
Ivanova *et al.*,[106]	30 days	Baseline and post-intervention	Twenty-one healthy subjects (15 female/ 6 males; mean age, 25.2 ± 10.7 years; mean BMI, 23.1 ± 6.0 kg/m^2)	Elderberry drink (200mL/day) Composition (200mL): Total polyphenols: 45.32 mg QE; ACNs: 3.66 mg CGE; Antioxidant capacity: 1.45 mmol (TAC assay)	None	Total serum antioxidant capacity Serum levels of total thiols group	Increase in total serum antioxidant capacity Increase in total thiols group
Johnson *et al.*,[107]	4-8 weeks	Randomized, double-blind, placebo-controlled parallel intervention	Forty-eight postmenopausal women with pre- and stage 1-hypertension Blueberry group: 25 females (mean age, 59.7 ± 4.58 years; mean BMI, 30.1 ± 5.94 kg/m^2) Control group: 23 females (mean age, 57.3 ± 4.76 years; mean BMI, 32.7 ± 6.79 kg/m^2)	Blueberry drink: freeze-dried blueberry powder (22 g) in 240 mL of water Composition (22 g): Phenolics: 844.58 mg; ACNs: 469.48 mg; Vitamin C: 2.27 mg; ORAC: 8.1 mmol TE	Placebo drink: macronutrient-matched control powder (22 g) in 240 mL of water Composition: no bioactive compounds	SOD serum levels	Increase in SOD serum levels
Bloedon *et al.*,[108]	8 weeks	Baseline and post-intervention	Ten untrained males (age range, 20-29 years; mean BMI, 27.0 ± 0.31 kg/m^2)	Fresh-frozen steam blanched and puréed wild blueberry (300g)	None	Manganese-SOD concentration in plasma Single DNA SBs in	No effect on manganese-SOD plasma concentration No effect on DNA

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				Composition: Not available		PBMCs	damage in PBMCs

Legend:5-OHMU: 5-hydroxymethyl-2′-deoxyuridine; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; ACNs: anthocyanins; AOPP: plasma levels of oxidation protein products; BMI: body mass index; CAT: catalase; CE: catechin equivalents; CGE; cyanidine 3-glucoside equivalents; dG: deoxyguanosine; Endo III: endonuclease III; FPG: formamidopyrimidine DNA glycosilase; FRAP: Ferric reducing antioxidant power; FW: fresh weight; GAE: gallic acid equivalents; GSH-Px: glutathione peroxidase; GST: glutathione S-transferase; HNE: 4-hydroxynonenal; LDL: low density lipoprotein; LH: lipid hydroperoxides; MDA: malondialdheide; MNBCs: mononuclear blood cells;ORAC: Oxygen radical absorbance capacity; Ox-LDL: oxidized LDL; SOD: superoxide dismutase; PBMCs: peripheral blood mononuclear cells; QE: quercetin equivalents; SBs: strand breaks; TAC: total antioxidant capacity; TAS: total antioxidant status; TBARS: 2-thiobarbituric acid reactive substances; TE: Trolox equivalents; TEAC: Trolox equivalent antioxidant capacity; TRAP: total radical trapping antioxidant parameter.

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Graphical abstract

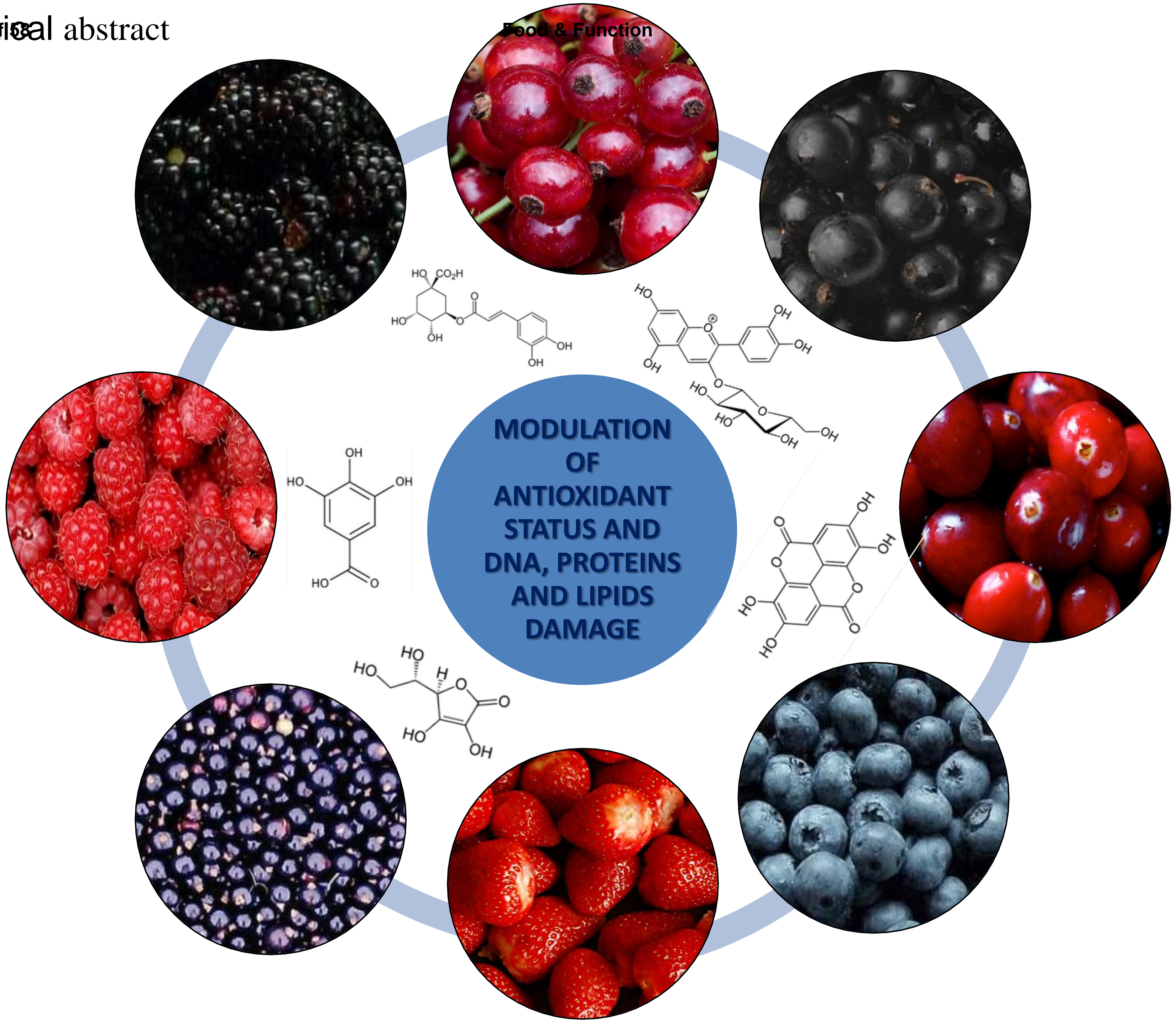

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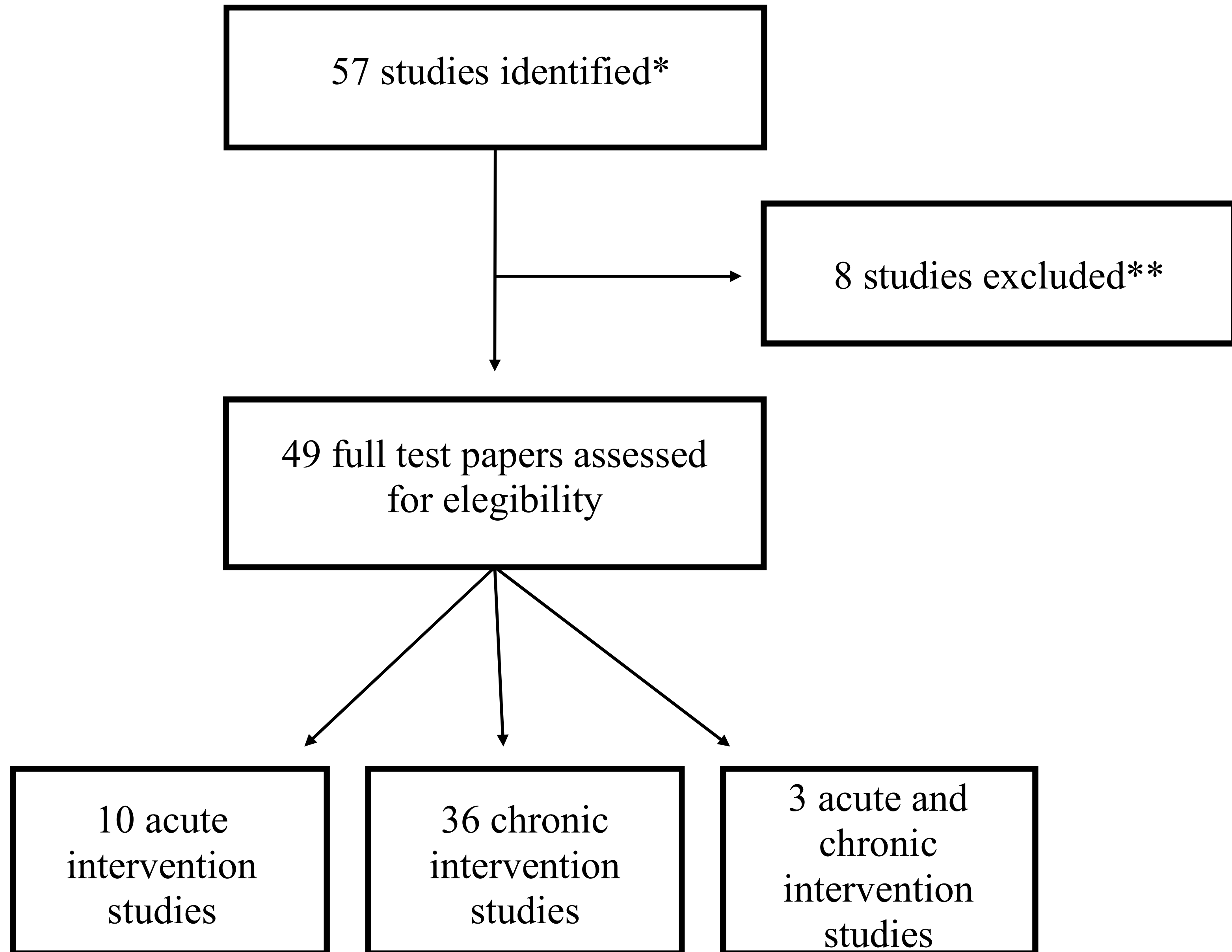
Figure 1



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