Odd chain fatty acids and odd chain phenolic lipids (alkylresorcinols): Essential for diet?

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Abstract

8   Odd chain fatty acids (C15:0 and C17:0) from dairy fat as well as odd chain phenolic

9   lipids (alkylresorcinols) from whole grain are commonly reviewed as candidate

10 biomarkers for dietary analysis and their ingestion are inversely related to chronic disease

11 risks. Therefore, low levels of dietary intake of these odd chain molecules may be related

12 to higher risk of physiological states that cause chronic diseases or mortality. It is a

13 prerequisite to examine and understand their main role in beneficial health effects in

14 disease prevention. We propose odd chain fatty acids (OC-FA) and most importantly odd

15 chain phenolic lipids (OC-PL) as potential essential dietary compounds since they play

16 key roles in physiological mechanisms. This review evaluates potential roles of OC-FA

17 and OC-PL in mitigating chronic diseases *in vitro* and *in vivo* studies to support our

18 hypothesis for odd chain molecules as essential dietary lipids. Further studies are needed

19 to investigate the relationship between reduced intake of OC-FA and OC-PL containing

20 foods and susceptibilities to chronic diseases.

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1. Introduction

Observational studies have shown an association of plasma odd chain fatty acids (OC-FA) with the consumption of dairy products, especially milk fat with lower risk of cardiometabolic diseases (Hodson, Skeaff, & Fielding, 2008; Kröger et al., 2010; Smedman, Gustafsson, Berglund, & Vessby, 1999). Similarly, epidemiologic studies have also shown an inverse relationship between consumption of whole grains and the risk of chronic diseases, and main contribution of this health benefits could be attributed to protection effects of phytochemicals such as alkylresorcinols. Alkylresorcinols are amphiphilic odd chain phenolic lipids; they play structural roles in the cell membrane including antioxidant, antibacterial, cytotoxic, genotoxic, and signalling properties. Their structural diversity and related biological activities have been reviewed (Kozubek & Tyman, 1999).

The aim of this review is to propose OC-FA and OC-PL as essential dietary lipids. OC-FA will first be discussed briefly in the following section; then OC-PL will be presented with their health beneficial effects in mitigating chronic diseases *in vitro* and *in vivo* studies to support our hypothesis for odd chain molecules as essential dietary lipids. Further studies are needed to investigate the relationship between reduced intake of OC-FA and OC-PL containing foods and susceptibilities to chronic diseases.

2. Odd chain fatty acids; C15:0 & C17:0

OC-FA are pentadecanoic (C15:0) and heptadecanoic (C17:0) fatty acids with an odd numbered acyl chain while OC-PL are phenolics with odd numbered alkyl chains. Their incorporation into cell membranes can enhance functionality by effecting membrane

53 fluidity. Odd chain saturated fatty acids have lower melting points that can increase

54 fluidity of cellular membranes than their lower even-numbered homologs (Kurotani et al.,

55 2017a).

56 Studies have linked increase in odd-chain saturated fatty acids concentrations with

57 reduced risk of coronary heart disease and diabetes. The EPIC-Norfolk prospective study

58 assessed the relationship between plasma phospholipid fatty acid concentration and

59 coronary heart disease in a European population and found that increased concentrations

60 of plasma odd chain phospholipid fatty acids resulted in a lower risk of coronary heart

61 disease (Khaw, Friesen, Riboli, Luben, & Wareham, 2012). The EPIC-InterAct case-

62 cohort study investigated the association of individual plasma phospholipid saturated

63 fatty acids and type 2 diabetes incidences in a European population. The study

64 demonstrated the inverse association of odd chain fatty acids C15:0 (pentadecanoic acid)

65 and C17:0 (heptadecanoic acid) and positive relationship of even chain saturated fatty

66 acids (C14:0, C16:0, and C18:0) with type 2 diabetes (Forouhi et al., 2014). Moreover, an

67 inverse association between longer chain saturated fatty acids (C20:0, C22:0, C23:0, and

68 C24:0) was found furthering the argument that all saturated fatty acids should not be

69 classified as adverse to health. A cross-sectional study Kurotani et al., (2017a) examined

70 the association of saturated fatty acids in serum phospholipid and circulating levels of

71 adipokines secreted from adipose tissue in Japanese population. Elevated levels of

72 C15:0 and C17:0 fatty acids were inversely associated with circulating levels of leptin

73 and PAI-1, both of which in high concentrations are associated with increased risk of

74 type 2 diabetes and cardiovascular disease.

75   Plasma OC-FA is causally associated with consumption of dairy products and humans

76   were previously thought unable to synthesize OC-FA, while cows can use propionyl-CoA

77   instead of actetyl-CoA for OC-FA synthesis (Weitkunat et al. 2017). However, a recent

78   study by Weitkunat et al. (2017) revealed that propionate production in the gut following

79   dietary fibre intake, such as inulin, can lead to OC-FA synthesis in humans. The study

80   showed evidence for a novel pathway for endogenous production of odd chain fatty acids

81   from gut derived propionate, a by-product of dietary fiber consumption. For 7 days

82   participants received daily doses of 30 g of either cellulose (control; non-fermentable

83   dietary fibre), inulin (fermentable dietary fibre), or propionate (3 carbon short chain fatty

84   acid). OC-FA were then determined in plasma phospholipids. Intake of inulin and

85   propionate increased plasma heptadecanoic (17 carbon fatty acid) by 11% ($P<0.01$) and

86   13% ($P<0.001$), respectively, and plasma pentadecanoic acid (15 carbon fatty acid) by ~

87   17% ($P<0.05$) and ~ 13% ($P=0.05$), respectively, while the non-fermentable cellulose had

88   no effect. The mechanism proposed for endogenous synthesis of OC-FA due to dietary

89   fibre consumption in humans is the absorption of gut derived proprionate through the

90   portal vein and transportation to the liver where it is converted to propionyl-CoA and

91   competes with acteyl-CoA for fatty acid synthesis. Since the starter unit for the fatty acid

92   synthase reaction has 3 carbons (propionyl-CoA) instead of 2 carbons (acetyl-CoA) the

93   product is an OC-FA.

94   In a very recent study, C15:0 has been proposed as a potential essential fatty acid that

95   attenuates inflammation, anemia, dyslipidemia and fibrosis *in vivo*, potentially by

96   binding to key metabolic regulators and repairing mitochondrial function (Venn-Watson,

97   Lumpkin, & Dennis, 2020).

2.1 The pathway of odd chain fatty acids

99   There is an inverse relationship between higher circulating concentration of OC-FA

100   (C15:0 and C17:0) and lower risks of cardiometabolic diseases, indicating lower

101   mortality with higher odd chain fatty acids consumption (Venn-Watson et al., 2020).

102   OC-FA, commonly found in dairy fat are produced by rumen microbial fermentation and

103   microbial *de-novo* lipogenesis (Vlaeminck, Fievez, Cabrita, Fonseca, & Dewhurst, 2006),

104   then transferred into the host animal (Jenkins, West, & Koulman, 2015). The microbial

105   *de-novo* lipogenesis consists of malonyl CoA condensation reactions with acetyl CoA

106   (starter molecule). Sequential condensation reactions yield mainly even numbered fatty

107   acids; hexadecanoic acid (C16:0) and less octadecanoic acid (C18:0); they are end

108   products of *de novo* lipogenesis. Two possible pathways for odd chain fatty acid

109   synthesis have been mentioned including either α-oxidation of even number fatty acids or

110   *de novo* synthesis from propionyl-CoA as starting molecules. More specifically, OC-FA

111   is produced by alpha carbon removal from the *de novo* lipogenesis end products (C16:0

112   or C18:0), followed by decarboxylation to produce either C15:0 or C17:0, respectively.

113   Those odd chain fatty acids in the animal rumen utilized by the mammary gland produce

114   milk fat, yielding 1.5-2.5% total odd chain fatty acids. Since C16:0 is relatively abundant

115   compared to C18:0 during *de novo* lipogenesis, the ratio of C15:0 to C17:0 is ~ 2:1

116   (Jenkins et al., 2015).

121   ### 3. Odd chain phenolic lipids; (alklyresorcinols)

122   Phenolics/polyphenols are secondary plant metabolites and they act as a natural defense

123   mechanism providing protection against external damages (Agil & Hosseinian, 2012b).

124   ARs belong to a large group of phenolic lipids that differ mainly by the odd-numbered

125   hydrocarbon chain attached to position 5 on the benzene ring (Kozubek & Tyman, 1999).

126   Structurally, ARs consist of 1, 3-dihydroxy-5-alkylbenzene (5-alkylresorcinol) and is

127   alkylated at position 5 by mostly a saturated, odd numbered hydrocarbon side-chain

128   containing 13-27 carbon atoms. The structure of ARs can vary according to the degree of

129   unsaturation, chain length, ring or chain substituted functional groups on the alkyl chain

130   or aromatic ring, and position of the alkyl chain (Kozubek & Tyman, 1999; Ross, Kamal-

131   Eldin, & Åman, 2004). These isoprenoid OC-PL are present as mixtures of several

132   homologues and derivatives. ARs occur in high amount in rye (Ross et al., 2003b), wheat

133   (Kulawinek, Jaromin, Kozubek, & Zarnowski, 2008), and triticale (Ross et al., 2003b),

134   with the lowest levels reported in barley (Andersson et al., 2008; Ross et al., 2003b).

135   Phenolics in plants can act as natural antioxidants by preventing oxidation of foods,

136   enhancing their shelf life. Whole grain cereals are main sources of energy, protein, and

137   fiber in the world. Their beneficial health effects depend on how they are consumed;

138   refined or whole grain. Nowadays, they are mostly consumed in refined forms, and large

139   amount of bioactive components are removed in the bran or germ during milling

140   (Landberg et al., 2019).

141

3.1 The pathway of phenolic lipids (alkylresorcinols)

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143 Shikimate and polyketide (acetate) are the two main pathways of phenolic compounds

144 synthesis. The first pathway forms phenylpropanoids like hydroxycinnamic acids and

145 coumarins, and the second produces simple phenols leading to quinones formation

146 (Kozubek & Tyman, 1999). At the same time, the largest group of phenolics (flavonoids)

147 are formed through a combination of both pathways. Resorcinolic lipids are derived from

148 the polyketide (acetate) pathway by 2`-oxoalkylresorcylic acid synthase (ORAS), a type

149 III polyketide synthase (Yu, Xu, Zeng, & Zhan, 2012). The acetate pathway starts with

150 polyketomethylenic chains $(CH_2-C)_m$, which is derived from acetic acid, the activated

151 forms of acetyl-S-CoA and malonyl-S-CoA (Birch & Donovan, 1953). Both polyketide

152 and fatty acid pathways are similar since the formation of linear chains occurs by the

153 addition of C_2 units. A fatty acyl CoA reacts with malonyl CoA three times to form a

154 tetraketide intermediate by aldol condensation type reactions (Funa, Ozawa, Hirata, &

155 Horinouchi, 2006). The odd numbered ARs side chain is the direct result of the fatty acid

156 precursor (Suziki, kurano, Esumi, Yamaguchi, & Doi, 2003). The intermediate compound

157 undergoes an aldol condensation type ring closure and hydrolysis to release the CoA to

158 form an alkylresorcylic acid. The next step follows non-enzymatic decarboxylation to

159 yield 5-n-alkylresorcinols (Figure 1) (Baerson et al., 2010).

160   **3.2 Pharmacokinetics of OC-PL (ARs)**

161 The primary pharmacokinetic data in the literature comes from alkylresorcinols. Since OC-FA

162 share similar structures with phenolics lipids (alkyl chain and phenol head group), they

163 presumably follow similar absorption, distribution, metabolism and excretion. Generally

164 humans absorb approximately 60% of ingested alkylresorcinols by the small intestine via the

165 lymphatic pathway (Linko et al., 2007; Ross et al., 2003a). However, about one-third of

166 alkylresorcinols can be absorbed through the portal vein and metabolized to DHBA and

167 DHPPA by the liver before entering circulation (Marklund et al., 2014). Alkylresorcinols are

168 absorbed and transported in chylomicrons through the lymphatic system, bypassing the liver,

169 and enter circulation intact where they are incorporated into erythrocytes or present in

170 lipoproteins (Linko & Adlercreutz, 2007). They are then circulated to the liver where they

171 either undergo phase I or phase II metabolism or are repackaged into lipoproteins with higher

172 proportions found in HDL and VLDL compared to LDL (Linko-Parvinen, Landberg,

173 Tikkanen, Adlercreutz, & Peñalvo, 2007; Marklund et al., 2014). From circulation they can

174 also be stored in adipose tissue with longer chain derivatives having a higher affinity to

175 adipose cells compared to their shorter chain homologues (Jansson et al., 2010). In the liver,

176 metabolism of fatty acids similar to alkylresorcinols are initiated by cytochrome P450

177 dependant ω-oxidation. The two-step oxidation converts the hydroxyl group to a carboxylic

178 acid thereby shortening the alkyl chain through several β-oxidation rounds producing

179 hydrophilic DHPPA and DHBA as phase I metabolites which can further be conjugated

180 through phase II metabolism (Marklund, McKeown, Blumberg, & Chen, 2013). From the

181 liver, these metabolites are either secreted via bile to the intestine, where they are either

182 reabsorbed or excreted through feces, or secreted into plasma and eliminated via kidneys to

183 urine (Marklund et al., 2014).

184   **3.3 Bioactivity of Alkylresorcinols (ARs)**

185 ARs are well known for their bioactivity such as antimicrobial, antibacterial, antifungal, and

186 antitumor (Kozubek & Tyman, 1999). Their presence in biological membranes and

187 lipoproteins may provide antioxidant protection by anchoring the alkyl chain into the lipid

188 bilayer and stabilizing their free radical ; incorporating themselves directly in the membrane

189 (Ross, Kamal-Eldin, & Åman, 2004). Phospholipids in membranes have an alkyl chain ~18

190 carbons (Gropper, Smith, & Groff, 2005).

191 The fat-soluble nature and structure of phenolic lipids enable them potentially to cross the

192 blood brain barrier. There has yet to be a study proving this concept but multiple *in vitro*

193 studies have shown their potential beneficial effects on pathologies of the nervous system.

194 In a study (Rania et. al., (2016), mice fed a high fat (HF) diet supplemented with 0.5% AR

195 and 0.5% triticale bran extract showed a significantly improved antioxidant status ($p<0.05$) in

196 liver and heart tissues compared to control mice fed a non-supplemented HF diets. Moreover,

197 the level of reduced glutathione (GSH) content increased and the ratio of oxidized glutathione

198 to reduced glutathione (GSSG/GSH- a significant marker of oxidative stress) decreased in

199 heart and liver tissues of mice fed the HF- AR supplemented diet as shown in Figure 2. These

200 results are significant since high fat diet causes oxidative stress through increased levels of

201 reactive oxygen species. The improved antioxidant status with AR supplementation indicates

202 AR's ability to provide protection against oxidative stress in various body tissues. Further

203 studies are required to establish the mechanism of action responsible for this added protection.

204

205 Ross et al. (2004a) reported elevated γ-tocopherol levels in the liver and lungs of rats fed

206 purified rye ARs at concentrations reflecting levels similar to whole-grain rye (1g/kg) and rye

207 bran (4g/kg). Rats fed the highest concentration had 47% less liver cholesterol ($P<0.001$) and

208   35% less cholesterol in liver lipids (P<0.05) compared to the control diet. The study also

209   showed that the effect of alkylresorcinols on γ-tocopherol levels may be mediated through

210   competitive inhibition of the γ-tocopherol eliminating pathway.

211   In a cell line study Gliwa et al. (2011) PC-12 AC cells were treated with an extract of the

212   outermost fraction of Hazlet rye, containing high amount of ARs (1598 µg/g), and MTT cell

213   viability determined to measure mitochondrial activity and biogenesis. AAPH was added as a

214   free radical generator to determine the cytoprotective effect of the rye extract on metabolic

215   activity. Metabolic activity increased significantly when cells were treated with the outermost

216   fraction of Hazlet rye extract in the presence of AAPH, returning the activity to a normal state.

217   Furthermore, mitochondrial biogenesis increased when cells were treated with the extract. The

218   treatment of the cells with the extract presumably increased mitochondrial efficiency by

219   producing more ATP, fuel required for cell function, simultaneously reducing ROS, a by-

220   product of mitochondrial activity, thus resulting in a more efficient use of oxygen.

221   A recent of Meshginfar et al. (2020) has reviewed the pathways and mechanisms associated

222   with the pathogenesis of Alzheimer's disease and the modulatory effects of phenolic lipids on

223   these pathways (Meshginfar, Tavakoli, Dornan, & Hosseinian, 2020). This study emphasizes

224   the multi-dimensional influences of phenolic lipids roles in membrane incorporation and

225   protection; potential in combating Alzheimer's disease. Main factor in Alzheimer's disease is

226   the deficiency in cholinergic neurotransmission via the neurotransmitter Acetylcholine (ACh).

227   Also the enzyme breaking down ACh extracellularly (AChE) could be integrated in to

228   amyloid aggregates and causing to the formation of stable AChE-induced B-amyloid

229   complexes. The most importantly AChE could be inhibited due to the hydrophobic properties

230   of the inhibitors and their cationic nature of alkyl side chains (phenolic compounds) (Figure

231   3).

3

232 Beta-amyloid plaque, known as a second major agent to initiate Alzheimer pathogenesis,

233 accumulates outside of the neurons of the cerebrum (extracellular accumulation). Since the B-

234 amyloid protein is originated from the excision of an extracellular integral membrane protein

235 (APP-Amyloid Precursor Protein) (Groemer et al., 2011). As shown in Figure 4, the

236 incorporation of phenolic lipid into the cell membranes is one of the possible inhibitory

237 effects on formation of acethylcholin esterase-Acetyl choline complex (Meshginfar et al.,

238 2020).

239
240 In the study of Kurotani et al (2017), odd chain fatty acid (eg. Pentadecanoic acid C15:0) has

241 enhanced leptin delivery to its membrane receptors (OB-Rb) as well as higher efficiency in

242 receptor binding (Kurotani et al., 2017b). Leptin could bind to Janus kinase receptors through

243 JAK/STAT pathway that brings an increased level of peroximose proliferator-activated

244 receptor-c (PPARs- modulator of amyloid aggregation) (Greco, Sarkar, Johnston, &

245 Tezapsidis, 2009). It has been reported that odd chain phenolic lipids could show a similar

246 improvement of leptin due to their unique hydrophobic alkyl chain (Stasiuk, Kleta, &

247 Kozubek, 2011) (Figure 4).

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251 The Table 1 summarizes all the studies carried out in our research laboratory since 2011 at

252 Carleton University, Chemistry Department. Based on outcomes of those mentioned studies, it

253 can be supposed that ARs may serve as a preventive measure against oxidation linked with

254 high fat diet and obesity (Agil et al., 2016); higher AR content provides higher protection

255 against free radical damage (Gliwa et al., 2011).

4

3.4 Studies related to bioactivity-defense mechanism

256

257 Diet and lifestyle can be the most important factors effecting the occurrence and development of

258 neurodegenerative diseases as reported in a recent systematic review (Solfrizzi et al., 2017).

259 Neurodegenerative diseases such as Alzheimer's disease and Parkinson diseases, generally result

260 from oxidative stress and mitochondrial dysfunction causing pathological processes, including

261 loss of dopamine neurons (Zeng et al., 2019). For instance, a recent meta-analysis showed

262 significant association between Mediterranean diet and a reduced risk of major chronic

263 degenerative diseases, including Alzheimer's disease (Sofi, Macchi, Abbate, Gensini, & Casini,

264 2010).

265 Many studies confirm that consumption of whole grain decreases the risk of chronic diseases

266 such as obesity, diabetes, breast cancer, and cardiovascular diseases (Pauline & Rimm, 2003;

267 Sytar, Bośko, Živčák, Brestic, & Smetanska, 2018). In addition, lower whole grain consumption

268 has been associated with a higher risk of cognitive impairment in older aged people (Ozawa,

269 Shipley, Kivimaki, Singh-Manoux, & Brunner, 2017).

270 Recently, wheat alkylresorcinols protected human epithelium cells (ARPE-19) from oxidative

271 stress induced cell damage (Wang et al., 2019). This protection could be through Akt-dependent

272 Nrf2/H)-1 signalling; induced in a dose-dependent manner.

273 As shown in the Table 2 the neuroprotective effect of AR-C17 homologue against (H2O2)-

274 induced apoptosis and mitochondrial dysfunction in PC-12 cells suppressed oxidative damage

275 and mitochondria mediated apoptosis via the SIRT3/FOXO3a signalling pathway (Liu et al.,

276 2020).

277   A hospital based case study (*n*=990) (Sun et al., 2019) found an inverse relation with ischemic

278   stroke risk and plasma metabolites of ARs (DHPPA-3-(3,5-dihydrophenyl)-1-propionic acid).

279   This study provides further evidence to support the health benefits of whole-grain consumption.

280   All reported studies in Table 2 support our hypothesis "OC-PL need to be essential in diet."

4. Key regulated pathways in fat cell metabolism

More than 150 diseases have been linked to lipids, such as obesity (Manninen et al., 1992), type 2 diabetes (Investigators, 2003), cancer (Vlaeminck et al., 2006), neurological disorders (Reitz, Tang, Luchsinger, & Mayeux, 2004), high blood pressure and artery plaque (Miettinen, Railo, Lepäntalo, & Gylling, 2005). Many studies carried out in the fatty acid metabolism emphasis on even numbered fatty acid chains (C2 to C26), representing over 99% of human plasma total fatty acid concentrations (Hodson et al., 2008). At the same time, there is also low concentration of four odd chain fatty acids in human tissues; C15:0, C17:0, C17:1 (Çoker, de Klerk, Poll-The, Huijmans, & Duran, 1996), and C23:0 (Phillips & Dodge, 1967). Investigations of these OC-FA attract interests in the research community since they are used as internal standards in quantitative analysis; act as biomarkers for dietary intervention studies, type 2 diabetes and coronary heart diseases; and can be evidence for alternate endogenous metabolic pathways (Jenkins et al., 2015).

ARs have been reported to reduce or inhibit triglyceride accumulation (Andersson, Dey, Holm, & Degerman, 2011) beside their anti-inflammatory properties and antioxidant protection (Gliwa, et al., 2011). ARs addition in diet can prevent the risks of obesity and glucose intolerance (Oishi et al., 2014) and help increase insulin sensitivity and cholesterol excretion. This is one of very few studies that have investigated the physiological effects of ARs.

Understanding of fat cell metabolism will provide better understanding on body homeostasis and its function although information is limited on metabolic adipogenesis processes. Halama et al (2016) used metabolomics and transcriptomics approaches to determine crucial metabolic pathways related to fat cell metabolism in their study (Halama et al., 2016). They reported significantly regulated metabolites correlating with significantly regulated genes at different

304 stages of adipogenesis. Most specifically, the key identified regulated pathways were:

305 phosphatidlylcholines synthesis, even and odd chain fatty acids metabolism, and branched chain

306 amino acids (BCAA; leucine, isoleucine and valine) catabolism. The most interesting findings

307 were propionyl-CoA (a product of isoleucine degradation) determination as a putative substrate

308 for OC-FA synthesis and relationship between BCCA degradation products and intermediates of

309 the cholesterol synthesis. OC-FA and glycerophopolipids are mentioned as novel biomarkers of

310 adipogenesis. Previously it has been reported that OC-FA cannot be metabolised in the body and

311 only ingested by diet (Wolk, Furuheim, & Vessby, 2001), Halama et al. (2016) demonstrated that

312 OC-FA can be produced by adipocytes. Before it was only hypothesized that leucine could be

313 degraded into lipids and sterols (Rosenthal, Angel, & Farkas, 1974), in the study of Halama et al.

314 (2016), it was shown that leucine degradation product 3-hydroxy-3-methylglutaryl-CoA can play

315 a role as a substrate for cholesterol biosynthesis.

316

317 **5. Conclusion**

318 In this review, it was aimed to propose-first time- OC-PL as an active dietary lipid that prevents

319 chronic disease, potentially by providing antioxidant protection in biological membranes. Pairing

320 with our findings from Table 1 and literature outcomes (Table 2), here we suggest OC-PL (ARs)

321 as an active dietary fatty acid. Similarly, C15:0 (OC-FA) has already been suggested as an

322 essential dietary lipid by a recent study (Venn-Watson et al., 2020). Further studies are needed to

323 investigate the relationship between reduced intake of OC-FA and OC-PL containing foods and

324 susceptibilities to chronic diseases.

8

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Figure 1- The biosynthesis of phenolic lipids (alkylresorcinols) and various polyketide (triketide, tetraketide and pentaketide) resorcylic acids, adopted from Yu et al.(Yu et al., 2012)

Figure 2 Theoretical illustration of a hydroxyl radical (OH) scavenged by ARs incorporated in cell membrane (Agil & Hosseinian, 2012a)

521 **Figure 3** Cation- π interaction between phenolic lipid moiety (Eugenol) and tryptophan residue
522 of acetylcholinesterase (Wille et al., 2010).

523 **Figure 4** Schematic pathways of Alzheimer's disease that are affected by bioactivity of phenolic
524 lipid. Amyloid plaques are a consequence of β and γ secretase on amyloid precursor protein
525 (APP), then accumulation of the released amyloid beta (AB) pieces. Incorporation of phenolic
526 lipid into the cell membranes is one of the possible inhibitory effects on formation of
527 acethylcholin esterase-Acetyl choline complex (Meshginfar et al., 2020).

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