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Review

The Pharmacological Potential of Oil Palm Phenolics (OPP) Individual Components

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Abstract

The oil palm tree (*Elaeis guineensis*) from the family Arecaceae is a high oil-producing agricultural crop. A significant amount of vegetation liquor is discarded during the palm oil milling process amounting to 90 million tons per year around the world. This water-soluble extract is rich in phenolic compounds known as Oil Palm Phenolics (OPP). Several phenolic acids including the three isomers of caffeoylshikimic acid (CFA), *p*-hydroxybenzoic acid (PHBA), protocatechuic acid (PCA) and hydroxytyrosol are among the primary active ingredients in the OPP. Previous investigations have reported several positive pharmacological potentials by OPP such as neuroprotective and atheroprotective effects, anti-tumor and reduction in Aβ deposition in Alzheimer's disease model. In the current review, the pharmacological potential for CFA, PHBA, PCA and hydroxytyrosol is carefully reviewed and evaluated.

Key words: Caffeoylshikimic acid; Hydroxytyrosol; Oil palm phenolics; *p*-hydroxybenzoic acid; Protocatechuic acid; Shikimic acid

Introduction

The oil palm tree (*Elaeis guineensis*) from the family Arecaceae is a high oil-producing agricultural crop. The palm oil is extracted from the fleshy orange-red mesocarp of the oil palm fruit [1]. Palm oil is cultivated in about 43 countries globally, in which Indonesia and Malaysia are the top production countries. The growing needs of vegetables oil in replacing animal fats makes palm oil dominate other vegetables oil in the market. The cheapest price amongst vegetables oil, require less land utilization are the key reasons for palm oil being able to capture the global market [2].

In the oil palm industry, palm oil consists of 10% from the total production and another 90% is biomass which includes vegetation liquor [3]. Continuous research and development in the palm oil refineries, coupled with the advancement from the technology is fully utilized not only for the palm oil extraction but for other uses as well. Rapid development of palm oil industries and the increase of the palm oil demand leads to increase of the by-product and bio-wastes generated which includes empty fruit bunches (EFB), palm oil mill effluent (POME), sterilizer condensate, palm fiber and palm kernel shell [4]. A huge amount of bio-waste would give rise to the negative impact to the environment [5]. In the oil palm industry, large amount of vegetation liquor are discarded into the aqueous waste stream during the palm oil milling process, amounting to 90 million tons per year globally [5, 6]. A novel process to recover phenolic compounds from the aqueous waste stream were developed and resulting in producing a filtrate known as oil palm phenolics (OPP), containing high amount of phenolics [6-11].

Condensed from the literature, several positive attributes for OPP have been documented, particularly in pharmacological applications such as neuroprotective effects [12], atheroprotective effects [13], anti-tumor [14], and reduction in Aβ deposition in Alzheimer's disease model [15]. It has been

postulated that phenolic acids components found in the OPP, have promising potential for pharmacological applications. Thus, the aim of this review is to highlight the pharmacological potential of individual components of OPP which are caffeoylshikimic acid (CFA) as the major components and other phenolic acids include *p*-hydroxybenzoic acid (PHBA), protocatechuic acid (PCA) and hydroxytyrosol [6, 16]. The inclusion criteria of the literature selected for this narrative review is not restricted to only phenolic acids extracted from OPP or any oil palm products.

Caffeoylshikimic Acid (CFA)

CFA is one of the phenolics compound identified in the extraction of palm oil vegetation liquor in a form of a three different isomers. The isomers namely 3-O-caffeoylshikimic acid (3-O-CFA), 4-O-caffeoylshikimic acid (4-O-CFA) and 5-O-caffeoylshikimic acid (5-O-CFA) are identified as a signature phenolic acids group in the OPP. Throughout the literature, 3-O-CFA, 4-O-CFA and 5-O-CFA are also known as dactylifric, isodactylifric and neodactylifric, respectively are the main enzymic browning substrates present in dates [17]. In comparison to the other phenolic acids identified in OPP, CFA is the largest component, accounted for more than half of the total phenolics and serve as signature compound in OPP [6, 18]. To our knowledge, the pharmacological study of CFA as a whole compound is limited to no study in the literature.

The ability of CFA to be hydrolyzed into shikimic acid (SA) has received a great attention from many researches in identifying CFA from plants [19]. CFA can be hydrolyzed into caffeic acid (CA) and SA under appropriate conditions [18]. SA is a base material for the manufacturing of Oseltamivir phosphate (Tamiflu®), a drug used for prevention and treatment for the human influenza virus H1N1 from swine origin, seasonal influenza virus types A and B, and avian influenza virus H5N1 [20, 21]. To date, Chinese herbal star anise (*Illicium verum*) is identified as the primary source of SA for commercial production. This herbal preparation could produce up to the 17.14 % of SA on dry weight basis. Limitation arises when there is significant growing demand for Tamiflu® and the shortage of the SA supplies [21]. Shikimic acid isolated from the Chinese plant Star anise (*Illicium verneum*) is expensive, low isolation yield and limited availability is the major drawback in synthesizing this compound [22]. Thus, CFA can turns into one of the alternatives sources to recover SA.

Table 1 illustrates the summary of pharmacological activities of SA. Rabelo and co-workers [23] demonstrated the antioxidant and neuroprotective effects of SA using human neuroblastoma-derived SH-SY5Y cell line. They discovered that high concentration of SA can protects the cells against H_2O_2-induced oxidative stress and loss of viability. In their study, SA shows a significant antioxidant activity through total reactive antioxidant potential (TRAP), prevent lipid peroxidation induced by AAPH in thiobarbituric acid reactive species (TBARS) assay, inhibit hydroxyl radical (HO) production, inhibit SNP-induced nitrite production, inhibit the decrease in the sulforhodamine B (SRB) incorporation caused by H_2O_2 in SRB assay and decrease reactive species (RS) production in 2′,7′-dichlorohy-drofluorescein diacetate (DCFH-DA) oxidation assay. Another study conducted by the Rabelo and colleagues [24] reported the positive outcomes of the SA as a potential treatment to treat pro-inflammatory and painful conditions. In this study, they are using two different model which are murine macrophage cell line RAW264.7 and male Swiss mice. In the *in vitro* study, SA demonstrated a positive of anti-inflammatory properties by the decreasing of the pro-inflammatory cytokines, such as tumor necrosis factor (TNF) -α and interleukin (IL) -1β through inhibitory effect on extracellular signal-regulated kinase (ERK) 1/2 and p38 mitogen-activated protein kinase (MAPKs) phosphorylation. Meanwhile, their *in vivo* study reported that SA decreased formalin-induced nociceptive behavior, inhibited the inflammatory nociception induced by TNF-α and prostaglandin (PGE2) and eventually significantly attenuated the mechanical hyperalgesia induced by carrageenan and dopamine.

Veach and co-workers [25] reported the anti-thrombogenic potential of SA through the inhibition of platelet activation and aggregation by targeting the P2Y1/P2Y12-ADP pathway using *ex vivo* human blood sample. This study demonstrated the reduction of PAC-1 and P-selectin/CD62P expression, where both are the biomarkers of the various platelet activation. Additionally, the reduction in monocyte-platelet and whole blood platelet aggregation formation are also reported. Meanwhile, Park and colleagues [26] investigated the antithrombotic activity of SA both *in vitro* and *in vivo* model. SA possesses fibrinolytic activity through the decreasing of fibrin clot solution turbidity. The optimal pH for dissolving fibrin clots are in the acidic range indicates that this compound possess the fibrinolytic activity. Through the animal trial, ICR mice and SD rats model were used for the *in vivo* study. ICR mice are used to determine the anti-thrombolytic activity via carrageenan-induced

tail thrombosis model, and the anti-thrombotic effect of SA through collagen- and epinephrine-induced acute pulmonary thromboembolism model. Both results showed positive outcomes of anti-thrombotic effect of this compound. On the other hand, SA also attenuated thrombosis in the $FeCl_3$-induced carotid arterial thrombus in SD rats. Earlier study by Xing and friends [27] reported the protective effects of SA in acetic acid (AA)-induced colitis on rats animal model. In this study, rats treated with SA shows improvement in colonic damage. SA inhibited the elevation of myeloperoxidase (MPO), an enzyme used as a quantitative index of inflammation and inducible nitric oxide synthase (iNOS) activities. It also reduced oxidation products such as malondiadehyde (MDA) and nitric oxide (NO), and concurrently increased superoxide dismutase (SOD) activity, an enzymatic scavenger that acts as defensive agents against oxidative damage.

p-Hydroxybenzoic Acid

We now focus on PHBA, the second most abundant phenolic acid component in OPP after CFA. PHBA (or chemically known as 4-hydroxybenzoic acid) can be isolated naturally in a wide variety of plant sources such as carrots (*Daucus carota*), oil palm (*Elaeis guineensis*), grapes (*Vitis vinifera*) and virgin olive oil [28, 29]. This phenolic acid and its derivatives can be found naturally as well as synthesized chemically, possessing a range of biological activities such as anti-microbial, anti-hyperglycemic, anti-atherogenic, anti-inflammatory and antioxidant properties [30]. Additionally, the esters of PHBA (also known as parabens) are widely used as preservatives in food, cosmetic and pharmaceutical products. These PHBA esters which may be a methyl-, ethyl-, propyl- or butyl-paraben have proven to be very effective antimicrobial agents [31].

Table 2 illustrates the summary of pharmacological activities of PHBA. As far as we know, the study of pharmacological potential of PHBA (not included PHBA derivatives and esters) is currently very limited. Peungvicha and colleagues [32] demonstrated the anti-hyperglycemic potential of PHBA in normal Wistar rats through the reduction of plasma glucose level and the elevation of serum insulin level and liver glycogen content. This similar research group [33] also had conducted another study to demonstrate a possible mechanism of the hypoglycemic effects of PHBA in Wistar STZ-diabetic rats. In this study, results showed the hypoglycemic effects of PHBA through the reduction of plasma glucose level. However, the serum insulin level and liver glycogen content in diabetic model were not affected. They suggested that the hypoglycemic effect of PHBA was mediated through the increase in peripheral glucose consumption. Another study conducted by Cho and friends [34] reported a strong anti-microbial of PHBA activity against *S. aureus*, *L. mesenteroides*, *S. cerevisiae* and *C. albicans* through paper disc method at a concentration of 50 µg.

Table 1. Summary of pharmacological activities of shikimic acid.

References	Study Type	Experimental Model	Pharmacological Potential	Study Outcomes
[23]	*in vitro*	SH-SY5Y	Neuroprotective effects	Antioxidant activity in TRAP, inhibit lipoperoxidation in TBARS, inhibit HO, inhibit NO, inhibit SRB, ↓RS
[24]	*in vitro*	RAW264.7	Anti-inflammatory effects	↑cell viability, inhibit NO, ↓TNF-α, ↓IL-1β, inhibit ERK ½ and p38
	in vivo	Male Swiss Mice	anti-hyperalgesic	Inhibit nociceptive behavior, inhibit inflammatory nociception, attenuate mechanical hyperalgesia
[25]	*ex vivo*	Human blood sample	Anti-platelet and anti-thrombogenic	↓PAC-1, ↓P-selectin/CD62P , ↓monocyte-platelet aggregate formation, ↓platelet aggregation
[26]	*in vivo*	ICR mice and SD rats	fibrinolytic activity	↓fibrin clot solution turbidity, acidic pH
			Anti-thrombosis	Inhibit mouse tail thrombus formation, ↑survival rate, ↓thrombosis
[27]	*in vivo*	Male Sprague-Dawley rats	Ulcerative colitis	Improve colon damage, ↓MPO, ↓iNOS, ↓NO, ↓MDA and ↑SOD

Abbreviation: ERK, Extracellular Signal-regulated Kinase; HO, Hydroxyl Radical; IL-1β, Interleukin-1β; iNOS, inducible Nitric Oxide Synthase; MDA, Malondiadehyde; MPO, Myeloperoxidase; NO, Nitric Oxide; RS, reactive species; SRB, Sulforhodamine B; SOD, Superoxide Dismutase; TBARS, Thiobarbituric Acid Reactive Species; TNF-α, Tumor Necrosis Factor- α; TRAP, Total Reactive Antioxidant Potential

Table 2. Summary of pharmacological activities of *p*-hydroxybenzoic acid.

References	Study Type	Experimental Model	Pharmacological Potential	Study Outcomes
[32]	*in vivo*	Wistar normal rats	Anti-hyperglycemic	↓plasma glucose, ↑serum insulin, ↑liver glycogen
[33]	*in vivo*	Wistar STZ-diabetic rats	Anti-hyperglycemic	↓plasma glucose
[34]	*in vitro*	Food pathogenic bacteria, plant pathogenic bacteria, yeasts and plant pathogenic fungi	Anti-microbial	↑antimicrobial activity against *S. aureus, L. mesenteroides, S. cerevisiae* and *C. albicans*

Abbreviation: *C. albicans, Candida albicans; L. mesenteroides, Leuconostoc mesenteroides; S. aureus, Staphylococcus aureus; S. cerevisiae, Saccharomyces cerevisiae*; STZ-diabetic, streptozotocin-diabetic

Protocatechuic Acid (PCA)

Protocatechuic acid (PCA) or chemically known as 3,4-dihydroxybenzoic acid is a derivative of PHBA and naturally occurring phenolic acid. PCA is widely occuring in many edible plants such as olives (*Olea europaea*) [35], grapes (*Vitis vinifera*) [36], roselle (*Hibiscus sabdariffa*) [37], acai (*Euterpe oleracea*) [38]. Several investigations were carried out on PCA, its derivatives, and coforms (such as esters and aldehydes). PCA has been shown to possess a variety of pharmacological potential such as antioxidants properties [39], anti-cancer properties [40], anti-inflammatory properties [41] and anti-hyperglycemic properties [42]. The mechanism of action of PCA is primarily due to the antioxidant activity, including inhibition of generation, as well as free radical scavenging activities and up-regulating enzymes that involve in their neutralization [43]. Chronic inflammation and oxidative stress play a vital role in the pathophysiology of chronic diseases such as obesity, cardiovascular disease, diabetes mellitus and several types of cancer [44]. The pharmacological study of PCA as a whole compound in population is limited. However, there are a few other studies conducted in a population to determine the bioavailability of polyphenols including PCA after the consumption of fruits such as berries [45] and blood orange juice [46]. Additionally, Vauzour and colleagues [47] have demonstrated the moderate consumption of wine may improve vascular performance in healthy human volunteers. The positive effects of wine on improving vascular performance may be mediated by circulating wine-derived polyphenols including PCA.

Table 3 illustrates the summary of pharmacological activities of PCA. In oxidized low-density lipoprotein cholesterol (LDL-C)-induced insulin resistance mice model, Scazzocchio and colleagues [42] proposed that PCA might exert insulin-like activities by peroxisome proliferator–activated receptor-γ (PPAP*γ*) activation. PPARγ is a ligand activated nuclear hormone receptor that regulates glucose and lipid metabolism, and the transcription of proteins involved in glucose and fatty acid cellular uptake. For these reasons, PPARγ represents a main target for anti-diabetic drugs, such as thiazolidinediones (TZDs). Their findings provide evidence that PPAP*γ* might play a key role in the activation of its transcription factors and adiponectin, as well as glucose transporter type 4 (GLUT4) up-regulations. They concluded that PCA could be included into the preventive/therapeutic armory against pathological conditions associated with insulin resistance, such as type 2 diabetes and obesity. Lin and colleagues [48] studied the streptozotocin induced diabetic mice where they observed the PCA supplement could attenuate diabetic complications via its triglyceride-lowering, anti-coagulatory and anti-inflammatory effect. PCA not only improved glycemic control by reducing plasma glucose, triglyceride and total cholesterol while increasing plasma insulin levels, but also inhibited plasminogen activator inhibitor-1 (PAI-1) and fibrinogen levels. Anticoagulation factors antithrombin III (AT-III) and protein C plasma activities were also elevated. PCA treatments also reduced plasma levels of C-reactive protein (CRP), von Willebrand factor (vWF) levels, interleukin (IL) -6, tumor necrosis factor (TNF) -α, and monocyte chemoattractant protein-1 (MCP-1) levels in heart and kidney. Wang and co-workers [49] demonstrated that PCA was able to alleviate the formation of atherosclerosis in the ApoE-deficient mouse model. They postulated that PCA possesses the anti-atherogenic effect partially mediated via its anti-inflammatory mechanism. PCA treatment inhibited adhesion of monocytes to TNF-α, activated mouse aortic endothelial cells (MAECs) and nuclear factor-κB (NF-κB) *in vitro*. The vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) were also inhibited both *in vitro* and *in vivo*. NF-κB is a crucial transcriptional regulator of VCAM-1 and ICAM-1.

In their following study, Wang and friends [50] observed that PCA treatment reduced CC chemokine receptor 2 (CCR2) protein and mRNA expression in the mouse peripheral blood monocytes (PBMs) while inhibited mouse PBMs chemokine migration toward CC ligand-2 (CCL2) in a Boyden chamber. In the ApoE-deficient mouse model, oral administration of PCA decreased CCR2 protein and mRNA expression in PBMs while reduced thioglycollate-induced macrophage infiltration into the abdominal cavity. The anti-atherogenic property of PCA was postulated based on the reduction of monocyte/macrophage infiltration, at least in part via down-regulation of CCR2 expression in monocytes. Harini and collegues [43] demonstrated that PCA has an anti-hyperglycemic effect, which is evidenced by lowered plasma glucose and glycosylated hemoglobin (HbAlc) level. There was an elevation in plasma insulin and hemoglobin (Hb) along with the increased in the hexokinase activity and glycogen concentration. Glucose 6-phosphatase and fructose 1, 6-bisphosphatase actitvity were declined, followed by a reduction in adipose tissue and normalized pancreatic islets. They concluded that the administration of PCA possesses a potential anti-hyperglycemic effect that is comparable to a standard drug namely as glibenclamide.

Table 3. Summary of pharmacological activities of protocatechuic acid.

References	Study Type	Experimental Model	Pharmacological Potential	Study Outcomes
[42]	*in vitro*	human omental and murine cell line 3T3-L1 adipocytes	Antiglycemic	↑glucose uptake, ↑GLUT4 translocation, ↑adiponectin, ↑PPARγ activity, ↑adiponectin expressions, ↑GLUT4 expressions
[48]	*in vivo*	Male Balb/cA mice	Anti-inflammatory, anti-glycemic, anti-hyperlipidemia	↓plasma glucose, ↑insulin levels, ↓TG, ↓TC, ↓PAI-1, ↓fibrinogen, ↑AT-III, ↑protein C, ↓CRP, ↓vWF, ↓IL-6, ↓TNF-α, ↓MCP-1
[49]	*in vitro*	Mouse aortic endothelial cell (MAEC)	Anti-inflammatory and anti-atherosclerosis	↓monocyte adhesion to TNF-α activated MAECs, ↓VCAM-1 expression, ↓ICAM-1 expression, ↓NF-κB binding activity
	in vivo	apolipoprotein E (ApoE)-deficient mouse model		↓VCAM-1 and ICAM-1 expression, ↓NF-κB activity, ↓plasma-soluble VCAM-1 and ICAM-1, ↓aortic sinus plaque area, ↓cholesterol accumulation in aortas
[50]	*in vitro*	Isolated peripheral blood monocytes (PBMs) from ApoE-deficient mice	Anti-inflammatory and anti-atherogenic	↓CCR2 protein and mRNA expression, ↓mouse PBMs chemokine migration toward CCL2
	in vivo	ApoE-deficient mice		↓CCR2 protein and mRNA expression, ↓macrophage infiltration into the abdominal cavity
[43]	*in vivo*	male Wister albino rats	Anti-hyperglycemic	↓plasma glucose levels, ↑Hb, ↓HbA1c levels, ↑plasma insulin levels, ↑hexokinase activity, ↑glycogen content, ↓glucose 6-phosphatase, ↓fructose 1,6-bisphosphatase, ↓pancreas adipose tissue, normalized pancreatic islets within normal limit.
[51]	*in vivo*	Male Wister albino rats	Anti-hyperlipidemia	↓TC, ↓TG, ↓LDL-C, ↑HDL-C level
[52]	*in vitro*	RAW 264.7	Anti-inflammatory	↓TNF-α, ↓IL-1β, ↓NO, ↓PGE2, ↓iNOS, ↓COX-2, ↓IkB-*α* degradation, ↓NF-kB phosphorylation, inhibit nuclear translocation of p65, inhibit p38, ERK and JNK activation in MAPK pathway.
	in vivo	Male BALB/c mice		↓leukocyte number, ↓TNF-α, ↓IL-1β, ↓PGE2, ↓COX-2 , ↓NF-κB activation

Abbreviation: AT-III, Anticoagulation Factors Antithrombin III; CCR2, CC Chemokine Receptor 2; CCL2, CC Ligand-2; COX-2, Cyclooxygenase-2; CRP, C-Reactive protein; FFA, Free Fatty Acids; GLUT4, Glucose Transporter Type 4; Hb, Haemoglobin; HbAlc, Glycosylated Haemoglobin; HDL-C, High-Density Lipoprotein Cholesterol; ICAM-1, Intercellular Adhesion Molecule 1; IL-1*β*, Interleukin-1*β*; IL-6, interleukin- 6; iNOS, Inducible Nitric Oxide Synthase; LDL-C, Low Density Lipoprotein Cholesterol; MCP-1, Monocyte Chemoattractant Protein-1; NF-κB, Nuclear Factor-κB; PAI-1, Plasminogen Activator Inhibitor-1; PGE2, Prostaglandin E2; PPARγ, Peroxisome Proliferator–Activated Receptor-γ; TC, Total Cholesterol; TG, Triglycerides; TNF-α, Tumor Necrosis Factor-α; VCAM-1, Vascular Cell Adhesion Molecule 1; Vwf, von Willebrand factor

Borate and friends [51] conducted a study to determine the anti-hyperlipidemic effects of PCA on male Wister albino rats. In this study, they found that PCA are able to treat hyperlipidemia by decreasing the total cholesterol (TC), triglyceride (TG), low density lipoprotein-cholesterol (LDL-C) and increasing the high density lipoprotein cholesterol (HDL-C) at the end of the treatment. Min and co-workers [52] demonstrated the anti-inflammatory action of PCA on both *in vitro* and *in vivo* study. The RAW 264.7 macrophage cell line were used for the *in vitro* study where PCA decreased the pro-inflammatory cytokines namely TNF-α and IL-1β. Reduction of inflammatory mediators and enzymes, prostaglandin E2 (PGE2), nitrite (NO) expression, followed by the nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) level were also reported. On the other hand, they also conducted a study of carrageenan-induced inflammation in air pouches on male BALB/c mice. They observed that PCA treatment was able to reduce levels of protein content and leukocyte numbers, as well as inhibited the expression of TNF-α, IL-1β, PGE2 and COX-2. It is concluded that PCA may suppress the expression of TNF-α, IL-β, and COX-2 by regulating NF-κB and MAPK activations.

Hydroxytyrosol

Hydroxytyrosol is a phenyl ethyl alcohol type of phenolic compounds. It is chemically known as 4-(2-Hydroxyethyl)-1,2-benzenediol. It is widely found in the natural plants such as palm oil (*Elaeis guineensis*) [53] and olives (*Olea europaea*) [35, 54]. It can exist mainly as acetate, secoiridoid derivatives or free form [55]. It also obtains by biosynthesis from oleuropein occurred under aerobic and anaerobic conditions by using lactic acid bacteria [56]. Hydroxytyrosol is one of the phenolic compounds which can be found in olive oil. A few studies demonstrated the pharmacological potentials of olive oils including as a potential "natural adjuvant" in combination with chemotherapy treatment [57], inhibit enzymes associated with neurodegenerative disorders [58] and antidiabetic effects [29]. On the other hand, several studies have reported that hydroxytyrosol and its derivatives have antioxidant, anti-inflammatory and antimicrobial effects [55]. Recent studies have shown that it can also benefit from reducing the risk of cardiovascular disease, cancer and neurodegenerative disorders [59-61].

Table 3 illustrates the summary of pharmacological activities of hydroxytyrosol. Cardiovascular disease associated with some risk factors including high blood concentrations of TC, TG

and homocysteine, low HDL-C, hypertension, diabetes, and obesity [60]. The ability of hydroxytyrosol to improve lipid profile, reduce lipid oxidative damage and reduce blood pressure highlight the potential of this compound to reduce cardiovascular event risk [62, 63]. Hydroxytyrosol also possess a favorable effect on platelet function by inhibiting the production of eicosanoids and platelet aggregation, thus further improving cardiovascular event risk [64]. Based on the findings from the hyperlipidemic rabbit model, hydroxytyrosol is postulated to enhance the antioxidant status and reduced the size of atherosclerotic injuries [65].

Several studies demonstrated that polyphenols might have a potential effect against cancer. Hydroxytyrosol, one of the polyphenols has recently received particular attention to counteract the all cancer because of its antioxidant, anti-inflammatory, anti-proliferative and proapoptotic activities [66]. Phenolic compounds have high antioxidant activity and have been studied extensively as anti-tumor agent by inhibiting the proliferation of cancer cells and promoting apoptosis [59, 67]. Chronic inflammation and tumor growth are inter-correlated to induce the proliferation of cancer cells. The study showed that the inflammation contributes to 15–20% of all cancers [68]. Hydroxytyrosol has anti-inflammatory activity that demonstrates to its potential anti-carcinogenic activity. Indeed, hydroxytyrosol inhibits the transcription of the enzymes COX-2 and 5-lipooxygenase, reducing the prostaglandin E2 synthesis. This condition can prevent the cancer development [69]. Besides antioxidant and anti-inflammatory abilities of hydroxytyrosol and other polyphenols, numerous studies in the literature has suggested the anticancer effects of these compounds through the activation of molecular signaling pathways resulting in the inhibition of tumor cell proliferation and leading to cell apoptosis [70].

Oxidative and nitrosative stress can break the function and integrity of brain tissue. Dietary hydroxytyrosol intake may have neuroprotective effects against neurodegenerative diseases. The recent finding conducted by Wu *et al.* [71] demonstrated that hydroxytyrosol could cross the blood-brain barrier which can be the reason of this compound able to inhibit neuronal diseases. In this study, acteoside was metabolized immediately into hydroxytyrosol after intravenous administration. Hydroxytyrosol was found both in blood and brain and existed as an unchanged compound *in vivo* [71]. Schaffer *et al.* [72] conducted a study to determine the efficacy of hydroxytyrosol-rich extract in diminishing NO-induced cytotoxicity in murine-dissociated brain cells. The findings indicated that this phenolic extract could improve the cytoprotection of brain cells due to severe loss of cellular ATP and the depolarization in mitochondrial membrane [72]. Hydroxytyrosol is a primary degradation product of oleuropein. Oleuropein possess neuroprotective activity by forming noncovalent complexes with beta-amyloid peptide, which is a protein component of senile plaques. This protein is formed in several neurodegenerative diseases [73]. Another study by Gonzalez-Correa and colleagues [61] investigated in a model of hypoxia reoxygenation in rat brain slices to determine the possible neuroprotective effect of hydroxytyrosol. The study showed that hydroxytyrosol inhibited LDH (brain cell death marker) significantly which may have potential effects on neurodegenerative diseases.

Table 4. Summary of pharmacological activities of hydroxytyrosol.

References	Study Type	Experimental Model	Pharmacological Potential	Study Outcomes
[65]	*in vivo*	Hyperlipidemic rabbits	Cardioprotective effects	↓TC, ↓TG, ↑HDL-C, ↓atherosclerotic lesions, ↑antioxidant status
[63]	RCT human study	200 healthy male	Cardioprotective effects	↓TC, ↑HDL-C, ↓TG, ↓LDL-C, ↑oxidative stress market levels
[70]	*in vitro*	MCF-7 human breast cancer cells	Anticancer effects	↓cell viability, ↓cell number, ↑cell apoptosis, significant block of G1 to S phase transition manifested by the increase of cell number in G0/G1 phase.
[74]	*in vitro*	HL60 human promyelocyticleukemia cells, and colon adenocarcinoma cells HT29 and HT29 clone 19A.	Anticancer effects	↑apoptosis in HL60 cells Arrested the cells in the G0/G1 phase with a concomitant decrease in the cell percentage in the S and G2/M phases.
[59]	*in vitro*	MCF-7 human breast cancer cells	Anticancer effects	↓number of MCF-7 cells arrest in the G0/G1 phase, ↓expression peptidyl prolyl cis-trans isomerase Pin1, ↓G1 key protein level, ↓Cyclin D1 level, ↑C-jun level
[67]	*in vitro*	MCF-7 human breast cancer cells	Anticancer effects	Inhibited proliferation of MCF-7 cells
[72]	*in vitro*	PC12cells	Neuroprotective effects	Possess cytoprotective effects
	ex vivo	Mice		
[61]	*in vivo*	Hypoxia–reoxygenation in rat	Neuroprotective effects	↓LDH efflux

Abbreviation: HDL-C, High-Density Lipoprotein Cholesterol; LDH, Lactate dehydrogenase; LDL-C, Low-Density Lipoprotein Cholesterol; TC, Total Cholesterol; TG, Triglyceride

Conclusion

Each individual components of OPP have unique pharmacological potential in the prevention and treatment of various diseases such as neuroprotection, anti-cancer, cardioprotection and hypolipidemic effects. Single or in combination of all three phenolic acids into one OPP liquor would produce high pharmacological potential OPP liquor for the nutraceutical and pharmaceutical market. OPP extracted from bio-wastes of oil palm industry would provide an opportunity to transform a biowaste burden into a range of potential applications for health and wellness. This will realize the full potential of oil palm fruit, increasing its commercial output, reducing its wastage and negative environmental footprints as well as contributing towards significant cost-saving measure of the national healthcare budget.

Abbreviations

3-O-CFA: 3-O-caffeoylshikimic acid; 4-O-CFA: 4-O-caffeoylshikimic acid; 5-O-CFA: 5-O-caffeoylshikimic acid; AA: Acetic acid; AT-III: Anticoagulation factors antithrombin III; *C. Albicans: Candida albicans*; CA: Caffeic acid; CCR2: CC chemokine receptor 2; CCL2: CC ligand-2; CFA: Caffeoylshikimic acid; COX-2: Cyclooxygenase-2; CRP: C-reactive protein; DCFH-DA: 2′,7′-dichlorohy-drofluorescein diacetate; EFB: Empty fruit branches; ERK: Extracellular signal-regulated kinase; FFA: Free Fatty Acids; GLUT4: Glucose transporter type 4; Hb: Haemoglobin; HbAlc: Glycosylated Haemoglobin; HDL-C: High-density lipoprotein cholesterol; HO: Hydroxyl radical; ICAM-1: Intercellular adhesion molecule 1; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LDH: Lactate dehydrogenase; LDL-C: Low density lipoprotein cholesterol; *L. Mesenteroides: Leuconostocmesenteroides*; MAECs: Mouse aortic endothelial cells; MAPK: Mitogen-activated protein kinas; MCP-1: Monocyte Chemoattractant Protein-1; MDA: Malondiadehyde; MPO: Myeloperoxidase; NF-kb: Nuclear factor-κB; NO: Nitric oxide; NOS: Nitric oxide synthase; OPP: Oil palm phenolics; PAI-1: Plasminogen activator inhibitor-1; PBMs: Peripheral blood manocytes (PBMs); PCA: Protocatechuic acid; PGE2: Prostaglandin E2; PHBA: *p*-hydroxybenzoic acid; POME: Palm oil mill effluent; PPARγ: Peroxisome proliferator–activated receptor-γ; RS: reactive species; *S. Aureus*: *Staphylococcus aureus*; *S. Cerevisiae: Saccharomyces cerevisiae*; SA: Shikimic acid; SOD: Superoxide dismutase; SRB: Sulforhodamine B; STZ-diabetic: Streptozotocin-diabetic; TBARS: Thiobarbituric acid reactive species; TC: Total Cholesterol; TG: Triglycerides; TNF: Tumor Necrosis Factor; TRAP: Total reactive antioxidant potential; TZDs: Thiazolidinediones; VCAM-1: Vascular cell adhesion molecule 1; Vwf: Von willebrand factor.

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Competing Interests

The authors have declared that no competing interest exists.

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