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Review of Studies on Palm-Oil Consumption in Relation to Risk of Cardiovascular Diseases

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ABSTRACT

Background: A balanced-diet containing edible-oil has been advocated to have more of unsaturated fatty acid. The saturated nature of palm-oil (PO) has led to the recommendation that its consumption should be limited to avoid the risk of cardiovascular diseases (CVD). The purpose of this study was to investigate the claims and counterclaims of PO consumption and the risk of CVD from biochemical perspective. **Methods:** Relevant published peer-review articles on PO consumption associated with risk of CVD were sorted from Google Scholar, Scopus, Medline, and PubMed databases. Keywords, such as "palm-oil, cardiovascular diseases, and cholesterol" were used for the search. **Results:** Apparent in animal studies, 52.17% support the claim that PO consumption is associated with CVD, and has been attributed to its saturated nature. According to the reports, PO consumption by virtue of its saturated nature-elicited hypercholesterolaemia, which may result to CVD. Furthermore, PO consumption may instigate fatty liver, cause narrowing blood vessels and thickening aorta of the heart, and consequently non-alcoholic steatohepatitis, a serious condition that may lead to severe cirrhosis, thereby increase CVD risk. On the other hand, 47.83% refute such claims that PO consumption is not associated with CVD risk. Based on human studies, 45.45% and 54.55% support and refute, respectively the claims that PO is associated with CVD. **Conclusion:** PO consumption has shown to be associated with hypercholesterolaemia, elevated low density lipoprotein cholesterol, hence, could instigate CVD, even though no study convincingly establishes any relationship between PO consumption and the risk of CVD. Furthermore, consumption of repeatedly heated PO (deep-frying) may instigate oxidative stress, and consequently CVD.

Keywords: *Palm Oil; Cardiovascular Diseases; Cholesterol; Hypercholesterolemia*

Introduction

Adequate intake of nutrient dense food is vital for achieving optimal nutrition and fitness. Inappropriate food consumption may affect nutritional wellbeing, and consequently malnutrition like underweight, overweight, and obesity. The latter has raised concern in many parts

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of the world and has emerged as risk factors for cardiovascular diseases (CVD) (Kumar, 2019, Powell-Wiley *et al.*, 2021, Wilding and Jacob, 2021). Although studies have shown that the more belly fat, the more the increase risk of heart disease even in the absence of obesity (Powell-Wiley *et al.*, 2021). The CVD is a major public health problem and an underlying cause of death in many parts of the world (Cappuccio and Miller, 2016). It has attracted considerable attention, especially in developed countries and developing countries.

The disease and other non-communicable diseases (diabetes, respiratory disease, and cancer) of global concern are responsible for about one-third of all deaths globally (Amini *et al.*, 2021, Okoduwa *et al.*, 2013). It claims more lives than cancer (all forms of cancer) and respiratory diseases (Benjamin *et al.*, 2019). Of more than 54 million deaths recorded in 2013, 17 million deaths were attributed to CVD (Roth *et al.*, 2015), and 18.6 million deaths in 2019 (Virani *et al.*, 2021). It has been projected that CVD would be the cause of more than 23 million deaths globally by 2030 (Amini *et al.*, 2021). In 2016, CVD was responsible for 1 of every 3 deaths recorded in the USA (Benjamin *et al.*, 2019), and a quarter of all mortality in India (Prabhakaran *et al.*, 2016). It is more alarming in the developing countries as two-third of patients die from the disease (Cappuccio and Miller, 2016). Yet, no considerable attention has been received in these regions. CVD has many causes, though physical inactivity and dietary factors are greatly considered as risk factors for the disease, as such, disease prevention should strongly focus on lifestyle (Arnett *et al.*, 2019), with emphasis on daily physical activity and reduction in saturated fat consumption (Chen *et al.*, 2011). In the 60s and 70s, edible oils (including palm-oil (PO)) containing saturated fatty acids (SFA) gained depraved negative reputation of being associated with CVD, and this steered the need to replace PO with edible oils containing more unsaturated fatty acid (USFA) than SFA (Hinrichsen, 2016).

PO is edible oil with significant economic importance. It belongs to the genus *Elaeis* with two species: *E. oleifera* and *E. guineenis*. The latter is largely produced in Malaysia and Indonesia (Varkkey *et al.*, 2018), though its origin is traced back to West Africa, particularly Nigeria (Odia *et al.*, 2015). It has arrays of domestic and commercial applications (Kadandale *et al.*, 2019, Padfield *et al.*, 2019). Despite its economic importance, PO has remained a subject of concern in health and environment. The environment steered the move by the members of the European parliament (MEP) to phase out the use of PO due to the danger it poses on the environment and its inhabitant (humans and animals) (Meijaard *et al.*, 2020). The production of PO remains a source of livelihood to millions of people, so that a more realistically solution could be proffered than the discontinuous use of PO. The health implication on the other hand had lingered for decades, and still remains a subject of concern. In 2003, the world health organization (WHO) firmly declared that PO contributes to the risk of CVD (Ismail *et al.*, 2018), and is the largest leading cause of deaths globally (Unhapipatpong *et al.*, 2021). The association between PO consumption and the risk of CVD has become a subject of controversies, invalidating the general belief that PO consumption is associated with CVD. This study therefore provides an insightful investigation of the association between PO and CVD through the biochemical analysis of published research outcomes on claims and counterclaims based on human and animal studies.

Materials and Methods

Search approach: The search approach was developed to determine all relevant studies in English language, which assessed PO consumption and the risk of CVD among humans and animal studies. Published peer-reviewed research articles were identified from major databases, such as Google Scholar, PubMed, Scopus, and MEDLINE. The keyword combinations used for the search in this study were "palm-oil, CVD, hypercholesterolaemia, and hypocholesterolemia" and animal studies, and human studies for the retrieval of articles regarding PO consumption and

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the risk of CVD from the above mentioned various databases. Simple basic statistics on the percentage was performed by taking the frequency (number of articles) in each category (claims or counter claims) from both human and human studies divided by the total number of articles in each category. The study was conducted between June 15, 2020 and April 16, 2021.

Selection criteria: Articles from studies having relevant information (both from human and animal studies) on PO and the risk of CVD were screened for eligibility. Articles reported in English were included without restrictions on the country. Articles having misleading information from the title and/or abstract were excluded. Articles published in languages other than English were excluded without restrictions on the country.

Ethics statement: All articles considered in this study were those approved by an institutional ethics review committee; in addition, informed consent was obtained from all the participants where applicable. Ethics approval was not requisite for the current study since it was based on secondary data generated from the primary source.

Search outcome and discussion

The outcome of the search obtained from the databases is presented in **Figure 1**.

Claims

Evidence based on animal studies: The saturated nature of PO and the risk of CVD has been a subject of concern for decades. The results from trials could not provide a firm association between PO and the risk of CVD (Sun *et al.*, 2015). As the assertions of the risk of PO consumption still prevails, Go *et al.* (2015) examined comparative effect of PO and sunflower oil (SFO) on serum lipid profile and fatty liver of Sprague-Dawley (SD) rats. After subjecting the SD rats to 2.5 ml PO, Sunflower oil (SFO), and the mixture of PO:SFO (1:1)/rats/day, for 21 days, no significant difference was observed in triacylglyceride (TAG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels of the PO, SFO, and the mixture of the PO:SFO fed groups. However, PO was shown to accumulate in the liver of the PO fed rats, insinuating liver dysfunction, and may contribute to the risk of CVD (Go *et al.*, 2015). This suggests that PO consumption may contribute to the risk of CVD without necessarily influencing (increasing) the serum lipid profile. The study, however, failed to examine activities of serum amino transferases; aspartate amino transferase (AST) and alanine amino transferase (ALT) to ascertain liver dysfunction and the extent of the dysfunction. In contrast, albino rats subjected to 15% PO, SFO, and Niger seed oil (NGO) for eight weeks showed significantly, high levels of TC, HDL-C, LDL-C, and TAG in PO fed rats compared to the levels observed in SFO and NGO fed rats. The saturated nature of the PO could be responsible for the rise in the serum lipid profiles observed in the PO fed rats (Mekonnen *et al.*, 2018). The rise in the serum lipid profile may provoke CVD risk. As revealed in the study by Hoque *et al.* (2018), PO fed rats showed a significant decrease in TC, LDL-C, and HDL-C compared to rats fed with soybean oil (SBO), thereby opposing the believe that polyunsaturated rich oils lowers serum lipid profiles compared to the SFA-rich oils. The histopathological examination revealed that the PO fed rats developed fatty liver, narrowed blood vessels, and hardened aorta of the heart compared to the SBO fed rats (Hoque *et al.*, 2018). Fatty liver if not arrested would progressively result in a non-alcoholic steatohepatitis (NASH), a serious condition that may lead to severe cirrhosis (Jichitu *et al.*, 2021, Perdomo *et al.*, 2019). It has been reported that people with NASH are prone to CVD, especially stroke and coronary artery disease (Hagström *et al.*, 2019, Patil and Sood, 2017). NASH has been observed in mice fed 41% PO and hybrid PO (HBPO) for eight weeks, suggesting the need to embrace consumption of a low fat diet (Sales *et al.*, 2019). Also PO (3 ml/kg/day) for 6 weeks poses CVD risk, as evident by lipid-driven body inflammation, increased body and liver lipid accumulation and increased fasting serum triglyceride, thereby advocating that intake should

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not be more than 1 ml/kg/day (9.5 % of total cal/day or 3.2% of total food intake/day) (Naphatthalung *et al.*, 2018).

Furthermore, Spreafico *et al.* (2018) investigated the effects of excess intake of HBPO on serum lipid profile, hepatic total lipid content, and the expression of microribonucleic (miRNA) in marmoset. The marmoset was divided into two groups, containing ten (5 males and 5 females) each. Group 1 and 2 were given 41% of the HBPO and PO. The over consumption of the HBPO did not elicit significant changes in serum lipid profile compared to the PO fed group. However, the liver of the HBPO fed group increased in size (enlarges) as a result of excessive lipid accumulation, signifying NASH characteristics (Spreafico *et al.*, 2018). In addition to increasing the number of steotic cells as evident in hepatocellular lesion, HBPO modulates the expression of miRNA (Spreafico *et al.*, 2018), indicating that dietary fat influences the expression of miRNA (Casas-Agustench *et al.*, 2015, Parra *et al.*, 2010).

Repeated use of PO for frying (deep frying or repeated frying) is a common practice especially among the low-income earners. There is no other reason for such a practice than to cut expenses of food preparation. This practice (deep frying) may compound the health risk associated with PO. Studies have shown that consumption of deep fried PO correlates with elevated blood pressure (BP) (Jaarin *et al.*, 2011, Leong *et al.*, 2008, Ng *et al.*, 2012). Deep fried oil was tested on the activities of BP regulating enzymes (heme-oxygenase-1 and angiotensin-converting enzymes) on adult SD rats fed with 15% of fresh palm oil (FPO), PO heated once, twice, five times and ten times, for a period of six months. The SD rats fed repeatedly heated PO exhibits a significant decline in the activity of heme-oxygenase-1(HO-1) and overexpression of angiotensin-converting enzyme (ACE), with more effects observed in the group fed with PO reheated ten times (10x) (Xin-Fang *et al.*, 2012). Three isoforms of heme-oxygenases (HO-1, HO-2, HO-3) have been identified, but HO-1 is highly expressed in the spleen and tissue involved in hemoglobin degradation (Lee and Choi, 2019). HO-1(a rate limiting enzyme in heme catabolism) catalyzes oxidative cleavage of heme to biliverdin, free ferrous iron (Fe^{2+}) and carbon monoxide (CO) (Chou *et al.*, 2018). Biliverdin which is reduced to bilirubin by biliverdin reductase (Lee and Choi, 2019, Mhillaj *et al.*, 2019), plays an important role in attenuating the risk of CVD (Tsai and Tarng, 2019, Wang and Bautista, 2015). The CO on the other hand, regulates BP since it exhibits vasodilation property (Xin-Fang *et al.*, 2012), while ACE catalyzes the conversion of angiotensin-1 (Ang-1) to angiotensin-2 (Ang-2). The Ang-2 exhibits vasoconstriction property. Exposure to repeatedly heated PO may induce hypertension by decreasing the activity of HO-1 and increasing the activity of ACE (Xin-Fang *et al.*, 2012).

Similarly, Xian *et al.* (2012) studied the effect of 15% reheated PO on SD rats, which were divided into the groups, including control, fresh PO, five times heated and ten times heated PO, for a period of six months. The results showed that the tunica intima increased significantly in rats given ten times heated PO, indicating huge atherosclerotic plaque (Xian *et al.*, 2012). Deep frying of PO destroys its antioxidant (beta-carotene, tocopherol, tocotriols etc.) properties, and generates free radicals. The free radicals steered oxidative stress, and consequently atherosclerotic development (Nurul-Iman *et al.*, 2013, Xian *et al.*, 2012). In addition to the thickness of the tunica intima, changes in the tunica media of the aorta was also noticed (Xian *et al.*, 2012). A detailed study on changes in the tunica aorta of postmenopausal rats fed 15% repeatedly heated PO showed that fresh PO can protect the aorta which may be destroyed if repeatedly heated (Adam *et al.*, 2009). The heart pumps blood from the left ventricle into the aorta, and like other arteries, the aorta has several layers (including the tunica media and tunica intima) that ensure normal flow of blood. For instance, the tunica intima provides a smooth surface for the blood to flow, while the tunica media allows the aorta to expand and contract, with each heartbeat. Any structural modification of the aorta revealed in the SD rats exposed to the repeatedly heated PO,

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may be a predisposing factor for CVD (Xian *et al.*, 2012).

Evidence based on human studies: The biological similarities between rats and humans serve as (to some extent) the rationale for animal experiment so as to predict possible outcome in humans. However, data obtained from animal studies cannot be directly extrapolated and applied to humans. For this reason, the effects of PO on CVD outcome as revealed in animal studies may lack strong basis to mirror the health risk of PO in humans. It is also required to validate the claims using human subjects. Meta-analysis of clinical trials showed that, PO consumption results in higher LDL-C compared to vegetable oils low in SFA (Fattore *et al.*, 2014, Sun *et al.*, 2015). Also, a cross-sectional population study revealed the relationship between the types of cooking oils (PO and SFO) and serum TC in the adult population in a peri-urban area of Dares Salam. Out of 347 participants (age ≥40 year), 79% and 21% of the participants reported using PO and SFO, respectively, as their cooking oils. The mean serum TC of those using PO was significantly higher compared to the participant that uses SFO (Kakarmath *et al.*, 2017), suggesting the need to reduce or avoid the consumption of oils (including PO) rich in SFA. It has been suggested that imposing taxation on PO in countries with high PO consumption has been proposed as a policy to reduce death (Basu *et al.*, 2013). Similarly, Aung *et al.* (2018) investigated the effects of cooking oils (PO and Peanut oil), and the risk of non-communicable diseases (including CVD) in study participants (ages 20 to 74 years) of Yagon region of Myanmar. Of the 1372 participants, 681 were males and 691 were females. Among the male participants, PO users had a lower glucose levels and body mass index (BMI) than the peanut users. Among the female participants, PO users had a higher diastolic BP, TC, and TAG than the peanut users (Aung *et al.*, 2018). Compared to olive oil, PO increased TC and LDL-C among thirty healthy men with normal blood cholesterol levels (Tholstrup *et al.*, 2011).

The claims that PO consumption is associated with CVD, are centered (to a large extent) on its saturated nature (**Figure 2**). PO is made up of about 50% SFA and 50% USFA, with palmitic acid (PA) which is the major fatty acid in PO. The high content of PA in PO is the main reason that PO consumption is associated with CVD. The assumption became pronounced when diet-heart hypothesis was put forth, that is the assumption that diet rich in SFA, serum TC, LDL-C, and CVD are casually related (**Figure 2**). The hypothesis was transformed into public health policy (DuBroff and de Lorgeril, 2019). The policy focuses on CVD with emphasis on the reduction of SFA intake. In this study, a summary of some studies that support the claims that PO consumption is associated with CVD is presented in **Table 1**.

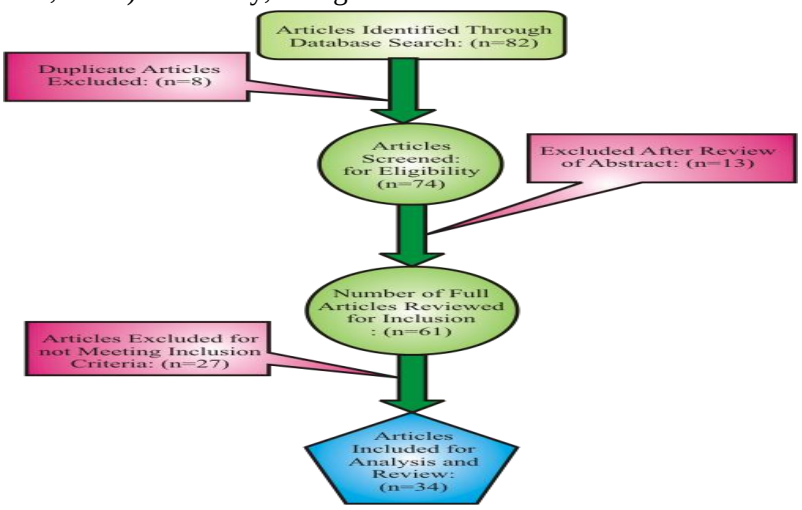

Figure 1. Flow diagram of articles that were identified, screened, met inclusion criteria, and analyzed in this study.

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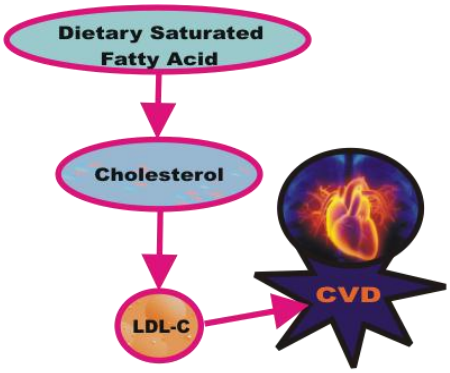

Figure 2. Schematic representation of the diet–heart hypothesis (Culled from Jurewitz, 2007, Aung et al., 2018)

Table 1. Studies with claims that PO consumption is associated with cardiovascular diseases.

Evidence from studies	Claims	Reference
Evidence from animal studies	PO administration to experimental rats induced hypercholesterolaemia, fatty liver, and may lead to CVD.	(Mekonnen *et al.*, 2018)
	HBPO is associated with liver enlargement, a characteristic of NASH which has been linked to CVD.	(Hagström *et al.*, 2019)
	Mice fed high fat diets exhibit NASH and may progress to liver cirrhosis, and consequently coronary artery disease and stroke.	(Patil and Sood, 2017), (Hagström *et al.*, 2019)
	Repeated use of PO is associated with hypertension. PO fed to experimental rats induced obesity, a risk factor for CVD. Repeated use of PO may instigate hypertension as evident in the thickness of the tunica intima, decreased and increased activities of HO-1 and ACE, respectively. Repeatedly heated PO causes oxidative damage thereby predisposing to atherosclerosis.	(Kamisah *et al.*, 2015) (Defo *et al.*, 2017, Xian *et al.*, 2012), (Kamisah *et al.*, 2015), (Xin-Fang *et al.*, 2012), (Adam *et al.*, 2008)
	Experimental rats subjected to 15% PO diet for 16 weeks induced obesity, a predisposing factor for CVD.	(Defo *et al.*, 2017)
Evidence from human studies	Population-based studies revealed that those who use PO frequently are at risk of CVD. Meta-analysis, and cross sectional population studies have shown that PO users had higher TC and LDL-C, compared to the nonusers of PO.	(Kakarmath *et al.*, 2017), (Sun *et al.*, 2015), (Kakarmath *et al.*, 2017, Tholstrup *et al.*, 2011), (Sun *et al.*, 2015), (Tholstrup *et al.*, 2011)
	The saturated nature of PO could be the cause of elevated rise in TC and LDL-C, and may potentiate CVD. Meta-analysis, and cross sectional population studies have shown that PO users had higher TC and LDL-C, compared to the nonusers of PO. The saturated nature of PO could be the cause of elevated rise in TC and LDL-C, and may potentiate CVD.	(Kakarmath *et al.*, 2017), (Sun *et al.*, 2015), (Tholstrup *et al.*, 2011)

PO: Palm oil, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, CVD: Cardiovascular diseases, HO-1: Heme-oxygenase-1, ACE: Angiotensin converting enzyme.

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Counterclaims

Contrary to the claims on the effects of PO and CVD risk revealed in studies involving animals and humans, studies have also shown to refute such claims. PO may exhibit a protective role against hyperlipidaemia and CVD (Ajiboye *et al.*, 2015).

Evidence based on animal studies: To ascertain the protective role of PO against CVD, Onyeali *et al.* examined the effect of 20% PO supplemented diet for 12 weeks in albino rats. Examination of the serum lipid profiles at intervals of 4, 8, and 12 weeks were taken into consideration. At the end of 12th week, a significant reduction in TC, LDL-C, and TC/HDL-C ratio (a useful index for possible CVD outcome) was noticed, compared to the 4th and 8th weeks, suggesting that PO consumption may lower the risk of CVD (Onyeali *et al.*, 2010). The study by Oladapo *et al.* compared atherosclerogenic risk of 10% deodorized bleached PO (DBPO) with SBO and olive oil in diabetic Wister rats, for eight weeks. Overall, DBPO had a lower lipid profile, as evident in higher HDL-C levels and lower atherogenic index, compared to the diabetic rats fed SBO and olive oil. This implies that DBPO may reduce health complications (e.g. CVD) associated with diabetes. Diabetes and other risk factors (smoking, hypercalcemia, infections, poor diets etc.) are associated with CVD (Woodward, 2019). However, no single factor on its own can sufficiently result to CVD (Oladapo *et al.*, 2017). Rauchová *et al*. demonstrated the effects of red PO supplementation on lipid profile and glucose levels in Wister rats with different thyroid status, and revealed that red PO supplementation does not increase blood lipid levels (Rauchová *et al.*, 2018). Similarly, Oluba *et al*. revealed that PO improve serum and liver lipid profile in rats fed a high fat diet, and may offer protection against lipid-related disorders (Oluba *et al.*, 2011).

Most of the PO (especially those sold in western world) is not usually consumed in its natural form, as they are often refined (bleached and deodorized). During these processes (bleaching and deodorizing), some of the active metabolites, such as beta carotene, alpha tocopherol may be completely lost or reduced, which raises the question of whether super olein (SO), red palm olein (RPO), and palm olein are associated with hypertension (Boon *et al.*, 2013). Spontaneously hypertensive rats treated with 15% SO, RPO, and palm olein oil supplemented diet for 15 weeks revealed a significant decrease in systolic BP compared to the untreated hypertensive group (Boon *et al.*, 2013). This entails that the oils (SO, RPO, and palm olein oil) could be used to attenuate rise in BP. The SO and palm olein are usually obtained from fractionation, bleaching, and deodorizing of crude palm oil (CPO), while RPO is obtained from pretreatment and deodorizing of CPO. The RPO retains 80% of its antioxidant contents and a higher degree of monounsaturated fatty acid compared to the CPO. Administration of RPO (0.2 ml/day) for three months was shown to suppress an elevated heart rate, enhancing heart function and coronary heart flow in spontaneously hypertensive rats (Katengua-Thamahane *et al.*, 2017).

Hypertension is a public health concern, characterized by serious complications, such as endothelial dysfunction, left ventricle remodeling, ventricular arrhythmias, and cardiac death (Katengua-Thamahane *et al.*, 2017). Findings from the experimental studies suggest that consumption of PO may mitigate complications associated with hypertension. There are many causes of hypertension; however oxidative stress has shown to play a critical role in the development of hypertension or worsening hypertensive disorder (Loperena and Harrison, 2017, Sousa *et al.*, 2019, Touyz *et al.*, 2020). For more clarity, more studies are required to elucidate the role of PO on oxidative stress induce hypertension, which is also perceived to be a cause of hypertension and other forms of CVD. Male Wister rats fed 2% cholesterol for 4 weeks, followed by supplementation with 200 µl of RPO/day for five weeks showed a significant decrease in myocardial infarct size elicited by cholesterol (Szucs *et al.*, 2011), suggesting RPO could be used to protect the

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heart against ischemia/reperfusion injury (Szucs *et al.*, 2011). Ischemia/reperfusion or simply reperfusion injury is a condition that involves tissue damage when blood supply returns to the tissue after a period of ischemia.

Evidence based on human studies: Patients with ischemia and other forms of CVD are usually advised to avoid foods (among which PO is often mentioned) that may raise cholesterol levels. Absalome *et al.* assessed serum lipid profile and lipoprotein of patients (mean age of 57 years) with ischemia, subjected to PO. The study involved 120 patients, divided into three groups, including consumers of refined PO, consumers of unrefined PO, and the control group. The findings revealed that in the consumption of PO (refined or unrefined), duration of consumption had no influence on serum lipoprotein profiles of the patients with ischemic heart disease (Absalome *et al.*, 2017). Similarly, Lv *et al.* examined the effects of dietary consumption of PO on CVD risk in healthy young adults. In the study, 88 healthy participants (male and female), age (20-40 years), BMI (18.5-23.9 kg/m^2), with no abnormal liver function, no family history of type 2 diabetes and any form of CVD, no cancer, no drug and alcohol addiction, not smoking, were included. The study was carried out for 16 weeks. After dietary intervention with PO, no change observed in the BMI and serum lipoprotein profiles, suggesting the absence of weight gain or fat deposit and CVD risk factor (Lv *et al.*, 2018). The intervention period (16 weeks) and small sample size (88 participants) were the major limitations associated with the study. Similar studies involving larger sample size and longer period of dietary intervention using PO is necessary to strengthen the validity of the claim.

Batai *et al.* studied 83 apparently healthy volunteers (aged 18-50 years), 43 of them were PO consumers (67 g/day), while 40 were considered control. Findings affirm that the consumption of PO has no effect on the risk of CVD (Bataï *et al.*, 2020) (**Figure 3**).

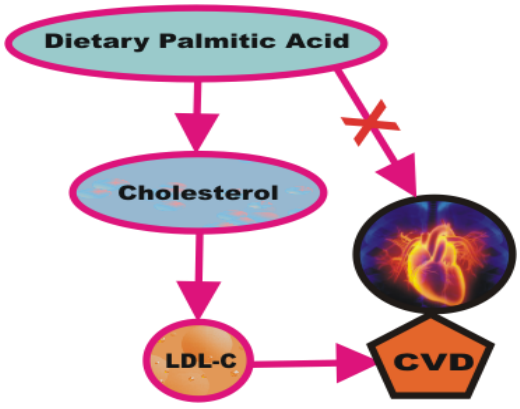

Figure 3. Schematic illustration of the relationship between saturated fatty acid (particularly palmitic acid) **and CVD** (Bataï *et al.*, 2020)

A meta-analysis inveterate that PO consumption results in the elevation of HDL-C and has no effect on TC, LDL-C, and TAG concentration and it may have no provocative health effect on CVD (Wang *et al.*, 2019). Interestingly, olive oil that is often considered the "gold standard" for the prevention of heart diseases was compared with hybrid PO (Lucci *et al.*, 2016). The study involved 160 participants assigned 25 ml hybrid PO or 25 ml extra virgin oil daily for 3 three months. The findings further strengthened the claim that hybrid PO, like olive oil could also be considered as gold standard for prevention of heart diseases (Lucci *et al.*, 2016).

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Contrary to the assumption that PO (due to its SFA content) is associated with CVD. Studies also revealed that SFA and CVD are poorly related (Zhu *et al.*, 2019). It is difficult to single out SFA (specifically PA) as a cause of CVD. Besides, not all patients with CVD appears to have increased TC and LDL-C levels and both TC and LDL-C appears unrelated to CVD (Ravnskov *et al.*, 2018). Till date studies have not clearly established the relationship between PA (a major SFA in PO) and the risk of CVD. A summary of some studies that counter claims of PO consumption associated with CVD is presented in the **Table 2**.

Table 2. Studies with counterclaims that PO consumption is associated with cardiovascular diseases.

Evidence from studies	Counter claims	Reference
Evidence from animal studies	PO fed to experimental rats lowers serum lipid profile.	(Oladapo *et al.*, 2017), (Onyeali *et al.*, 2010)
	PO administration is not associated with hypertension.	(Katengua-Thamahane *et al.*, 2017), (Boon *et al.*, 2013)
	PO could prevent the risk of CVD. Long term feeding of Wister rats with fresh red PO elicits no adverse effect on serum lipid profile. Feeding fresh PO to a Post-menopausal rat model showed no deleterious effect. The oil palm phenolic reduce atherosclerosis in rabbits.	(Szucs *et al.*, 2011), (Karaji-Bani *et al.*, 2006), (Kamsiah *et al.*, 2001), (Adam *et al.*, 2008), (Idris *et al.*, 2018), (Idris *et al.*, 2014)
Evidence from human studies	PO consumption had no influence (increase) on serum lipid profile.	(Bataï *et al.*, 2020), (Wang *et al.*, 2019), (Lv *et al.*, 2018), (Absalome *et al.*, 2017)
	HBPO, like olive oil, is also a gold standard in the protection and management of CVD.	(Lucci *et al.*, 2016)
	The study showed beneficial attributes of PO consumption among young population living in rural areas.	(Alexandre *et al.*, 2017)

PO- palm oil, TC- total cholesterol, CVD- cardiovascular diseases, HBPO- hybrid palm oil.

In normal physiologic condition, beta oxidation of PA may not elicit hypercholesterolemia. This is because metabolic processes operate under tight regulation, so that the body does not produce any metabolite (including cholesterol) beyond the physiologic need. The synthesis of every metabolite within the biological system has regulatory machineries. Cholesterol synthesis for instance, is regulated by the end product (cholesterol) by feedback inhibition of beta hydroxyl beta methyl glutaryl CoA (HMG-CoA) reductase, implying that the saturated nature of PO may not elicit over production of cholesterol, unless there is metabolic dysregulation (**Figure 4**). More studies are, however, necessary to elucidate whether or not PO consumption deregulate cholesterol synthesis pathway. The body is made up of billions of cells enclosed by cell membrane, of which cholesterol is an important component. People whose body cannot produce enough cholesterol, are advised to get enough from exogenous sources to avoid health complications, such as infertility, poor brain development, poor eyesight, and memory loss (Segatto *et al.*, 2019) associated with cholesterol deficiency.

Consuming fat exceeding physiological need, the excess is stored as TAG, although some fractions may be channel for immediate use. Upon physiologic requirement, the TAG is hydrolyzed by hormone sensitive lipase to glycerol and fatty acid. The latter is metabolized (via β-oxidation) to acetyl CoA, a precursor for cholesterol synthesis.

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Cholesterol is synthesized via several enzymatic steps, and regulated by feedback inhibition of HMG-CoA reductase by cholesterol. Such inhibition ensures that there is no more cholesterol synthesis, when cells contain enough cholesterol.

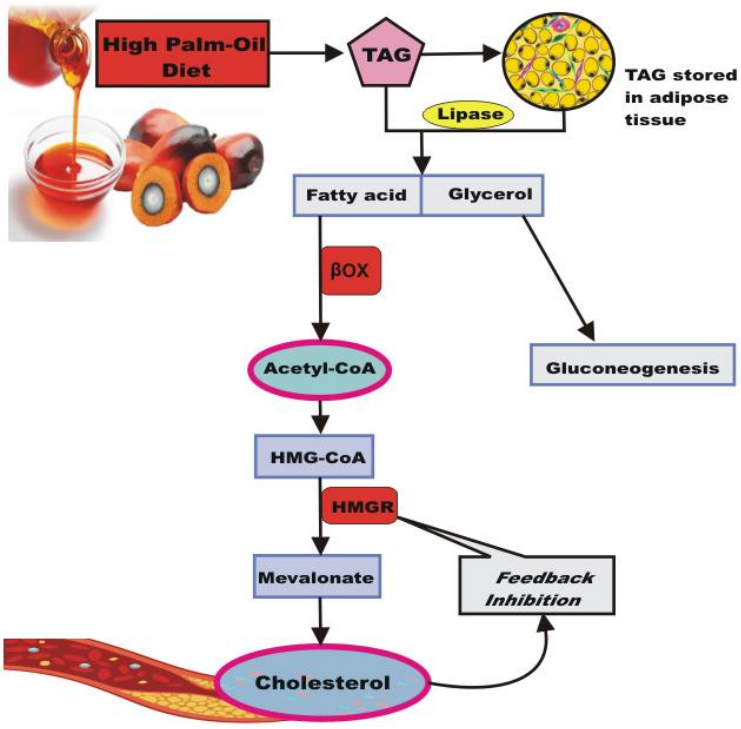

Figure 4. Feedback inhibition of cholesterol synthesis by cholesterol (Segatto *et al.*, 2019)

Furthermore, cholesterol is actively synthesized in the central nervous system, and any interruption of metabolic synthesis (especially in the newborns) may provoke normal brain function (Segatto *et al.*, 2019) and may lead to neurodegenerative disorders (Hussain *et al.*, 2019). Just as high cholesterol is associated with cognitive deficit (Martín *et al.*, 2014, Pushpendra and Jain, 2015), low cholesterol may also be associated with cognitive deficit, since high level cholesterol had been considered a potential protective factor against cognitive decline (Zhou *et al.*, 2018). To ensure normal cellular function, the balance between anabolism and catabolism (synthesis and degradation) of cholesterol must be tightly regulated (Sèdes *et al.*, 2018). Even though hypercholesterolemia correlates positively with CVD (in some individuals), no study has convincingly affirmed that hypercholesterolemia is an independent cause of CVD. No study has convincingly established that elevated level of LDL-C in some patients with CVD is as a result of PO consumption. Given that the nutritionally misleading term "bad cholesterol" is attached to LDL-C, the need to lower the so called "bad cholesterol" has been advocated. The study revealed that women who have lower LDL-C may be at greater risk of hemorrhagic stroke (Rist *et al.*, 2019), mortality from stroke, heart disease, cancer. (Nago *et al.*, 2011).

PO consumption (a good source of SFA) may be required for sustaining the working capacity of some cells. Many cells have preference for molecule (fatty acid, glucose, and amino acid) for cellular energy. For instance, the central nervous system (CNS) depends on glucose (about 60%) as a source of energy, while the heart derives energy (>70%) from fatty acid (Schulze *et al.*, 2016). The adipose tissue and skeletal muscle cells also derive their energy (to a large extent) from fatty acid (El Bacha *et al.*, 2010). The energy is usually derived

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from SFA than from USFA, unless the diet is devoid of SFA. The USFA (particularly linoleic acid and linolenic acids) are required for the synthesis of other important metabolites (eicosanoids) in the body. Although USFA may also contribute to the production of energy via its beta oxidation, the presence of SFA may spare USFA from such function (energy production) and rather used to produce the aforementioned metabolites (eicosanoids).

A significant limitation of the studies is the fact that none of the published literatures analyzed took cognizance of the type or age of PO consumed by the population investigated. The various dosages of PO which were reported were not in touch with the realities of food practice of humans. These limitations ultimately were considered impediment towards a conclusive judgment in this review paper. However, the strength in this study is that it provided the knowledge gap as contained in the analyzed data. It also provided a holistic retrospective study that investigated both human and animal studies that either reported the claim or counterclaim of PO consumption in relation to CVD. These contributions to knowledge can help researchers in their experimental design for further investigation of related studies in the future. The limitations observed in the reviewed articles would pave way for the design of better studies in the future.

Conclusion

PO consumption has shown to be associated with hypercholesterolaemia, elevated low-density lipoprotein cholesterol, and as such, assumed to be associated with CVD, even though no study convincingly establishes any relationship between PO consumption and the risk of CVD. However, consumption of repeatedly heated PO (deep frying) may instigate oxidative stress, and consequently CVD. More studies are necessary to elucidate whether or not PO consumption alters cholesterol synthesis pathway, and by what mechanisms.

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Authors' contributions

Abdulwaliyu I and Okoduwa SIR got the concept and design of the study. Abdulwaliyu I, Arekemase SO, Sangodare R, Muhammad A carried out the acquisition of literature materials and analysis. Arekemase SO, Sangodare R, Batari ML participated in the interpretation of data. Project supervision was by authors Okoduwa SIR and Muhammad A. Abdulwaliyu I drafted the manuscript. Revision and editing for intellectual content was by Okoduwa SIR and Aliyu M. All the authors gave a final approval of the revised manuscript for submission and publication.

Conflict of interest

The authors declare that there is no conflict of interest.

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