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EFFECTS OF OXIDISED OILS ON INFLAMMATION-RELATED CANCER RISK

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ABSTRACT

The practice of using cooking oils that are heated repeatedly is common to reduce the expenses of food preparation. However, this will result in lipid peroxidation, which generates compounds that are toxic to human health. Prolonged consumption of oxidised oils may affect lipid metabolism, which generates free radicals and products that will lead to pro-inflammatory pathways. A number of cellular, animal and clinical studies have revealed the effects of oxidised oils on inflammatory responses. By-products of lipid peroxidation, including trans, trans*-2,4-decadienal (2.4-De), 4-hydroxy-2-hexenals (4-HHE) and malonaldehyde (MDA) can be found significantly in samples treated with oxidised oils. Besides, the release of inflammatory biomarkers or cytokines will be induced due to the enhanced degree of oxidative stress. Inflammation has been acknowledged to be linked to increased risk of cancer. Therefore, the consumption of repeatedly heated oils, which have higher level of oxidation may potentially lead to cancer progression. The possible cancer risk induced by the dietary intake of pro-inflammatory oxidised oils, methodology considerations and limitations of studies related to cancer risk induced by pro-inflammatory oxidised oils will be discussed in this review.*

Keywords: oxidised oils, lipid peroxidation, oxidative stress, inflammation, cancer.

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INTRODUCTION

Deep frying is one of the most regularly used cooking methods worldwide. The consumption of deep-fried food is prevalent, particularly in developing countries. Highly oxidised lipids are consumed via dietary intake of these deep-fried foods. As large amount of edible vegetable oils are required during deep frying process, they are usually used repeatedly to ensure cost effectiveness (Leong *et al.*, 2015).

Frying oils heated at high temperature will lead to lipid peroxidation, followed by generation of toxic compounds such as *trans*-2,4-decadienal (2,4-De), 4-hydroxy-2-hexenals (4-HHE) and Malonadehyde (MDA) (Chang *et al.*, 2005; Boyd and McGuire, 1991). The range of frying temperature is advised to be between 160°C and 180°C as oils deteriorate more rapidly at higher temperatures while frying products absorb more oils at lower temperatures (Freire *et al.*, 2013). Repeatedly heating the oils will increase the degree of lipid peroxidation and thus exert adverse effects on health (Jaarin and Kamisah, 2012). Previous studies have reported that the consumption of oxidised oils will increase the risk of inflammation-induced diseases such as atherosclerosis, high blood pressure, gastric ulceration and cancers (Leong *et al.*, 2008; Obembe *et al.*, 2016). Furthermore, free radicals produced during lipid peroxidation may lead to oxidative stress, subsequently activate a number of molecular pathways that generate inflammatory molecules, such as interleukin 1 beta (IL-1β), interleukin 6

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(IL-6) and tumour necrosis factor alpha (TNF-α) (Patterson *et al.*, 2012). The production of these inflammatory molecules has been reported to have tumour-promoting effects, which is also associated to increased risk of cancers.

In this review, the mechanism and products of lipid peroxidation will be discussed. Besides, the inflammatory effects of oxidised oils will be reviewed based on previous research. The potential risk of cancers induced by inflammation due to intake of oxidised oils will also be discussed.

LIPID PEROXIDATION

Lipid peroxidation can be defined as the oxidative deterioration of lipids in which the oxidants, such as free radicals or non-radical species attack the carbon-carbon double bonds of lipids (Ayala *et al.*, 2014). This process encompasses the removal of hydrogen from a carbon, with the addition of oxygen molecule, producing lipid peroxyl radicals and hydroperoxides, which are the primary oxidation products (Choe and Min, 2006). The lipid oxidation process in oils can be increased by several intrinsic factors, for example, presence of pro-oxidants and antioxidants, fatty acid composition and water content, as well as external factors such as increased temperature, oxygen and light.

Rate of lipid oxidation is increased with the degree of unsaturation of the oil (Kris-Etherton and Committee, 1999). Due to the presence of double bonds, polyunsaturated fatty acids (PUFA) are more prone to oxidation compared to saturated fatty acids (SFA). The rate of oxidation of SFA was reported to decrease with increasing chain length (laurate > palmitate > stearate). In contrary, the rate of oxidation of unsaturated fatty acids was found to increase in the following order: linolenate > oleate > linoleate (Leyton *et al.*, 1987; DeLany *et al.*, 2000).

The primary oxidation products, such as: lipid hydroperoxides, are usually stable at moderate conditions, such as room temperature and without the presence of metals. However, the existence of metals or high temperature condition will cause them to be easily decomposed to alkoxy radicals and then generate secondary oxidation products (Choe and Min, 2006). Lipid peroxides and some of their bi-functional products may interact with the biological components, including enzymes, membranes and proteins, affecting vital cell functions (Frankel, 1984; Pizzimenti *et al.*, 2013). The decomposition of hydroperoxides usually takes place by the breaking of oxygen-oxygen bond (Pizzimenti *et al.*, 2013), producing alkoxy and hydroxyl radicals. Subsequently, the alkoxy radical will go through the process of homolytic β-scission of carbon-carbon bond, which results in the production of oxo-compounds and saturated or unsaturated alkyl radicals. It is followed by electron arrangement, addition of hydroxyl radical or transfer of hydrogen, generating the secondary lipid oxidation products (Choe and Min, 2006).

Secondary oxidation products are usually low molecular-weight molecules, such as aldehydes, alcohols, ketones and short-chain hydrocarbons (Choe and Min, 2006). Some of the secondary products are still unstable and will be further degraded to generate tertiary oxidation products, such as short chain free fatty acids (Lise Halvorsen and Blomhoff, 2011). The types of primary, secondary and tertiary lipid oxidation products are listed in *Table 1*.

The 4-Hydroxynomenal (4-HNE), as one of the examples of secondary oxidation product, is generated from the cleavage of omega-3 or omega-6 PUFA (Bremner *et al.*, 1997). Elevated amount of 4-HNE can be observed in plasma and many organs that undergo oxidative stress (Esterbauer and Cheeseman, 1990). Besides, MDA as one of the secondary products of lipid peroxidation in the cells, is generally used to determine the oxidative stress and antioxidant status of cancerous patients (Gaweł *et al.*, 2003).

BIOCHEMICAL INDICES

The oxidation level of oil samples can be assessed by performing biochemical tests. The biochemical indices that are generally used to determine the oxidation level of oils include peroxide value (PV), free fatty acid (FFA) value and *p*-anisidine value (*p*-AV), which will be discussed in this section.

TABLE 1. PRIMARY, SECONDARY AND TERTIARY PRODUCTS OF LIPID OXIDATION

Primary oxidation products	Secondary oxidation products	Tertiary oxidation products
Lipid hydroperoxides	Aldehydes; alcohols; ketones; hydrocarbons; esters; furans; lactones; epoxides; cyclic and hydroxyl deriatives of lipid hydroperoxides; monocyclic, biclyclic, aliphatic, dimeric and trimeric products of polymerisation or copolymerisation	Short chain free fatty acids

Source: Adopted from Dabrowska *et al*. (2015).

Peroxide Value

PV measures the concentration of peroxides formed during the primary stages of oxidation. It is generally used to determine the degree of rancidity of oils due to auto- and photo-oxidation, therefore it is useful to assess the extent to which spoilage has taken place (Kaleem *et al.*, 2015). In addition, it is widely used in quality control of oils. Oils with higher level of unsaturation are more prone to auto-oxidation (Mannekote and Kailas, 2012; Kaleem *et al.*, 2015). For instance, oleic acid (C18:1) which has higher degree of unsaturation compared to linoleic acid (C18:2) has been estimated to have lower susceptibility to oxidation (Yun and Surh, 2012).

The PV of oil samples can be altered by the condition of storage. Oil samples may be influenced by light, which induces photo-oxidation (Abdelmonem and Khogali, 2012). According to Anwar *et al.* (2007), PV of soyabean oil samples stored under sunlight increased significantly compared to those stored at ambient. Furthermore, the conditions and climate of the area where refinement process takes place have been reported to affect the oxidation level of oils, resulting in differences in PV (Kaleem *et al.*, 2015). In addition to that, longer storage time has also been found to increase the degree of oxidation of oil samples (Zahir *et al.*, 2017).

Besides, higher PV can be obtained in the oil samples reheated more frequently. Therefore, higher PV denotes reduced chemical stability of the oil samples (Leong *et al.*, 2015). During heating of oil samples, the trend of PV may be unstable as the hydroperoxides formed are very unstable and easily break down into various types of volatile and non-volatile products. Therefore, an increased level of PV of oil samples may appear at the beginning of heating process due to the high concentration of hydroperoxides formed, followed by a decreased PV level when secondary oxidation products are detected (Kaleem *et al.*, 2015). However, PV is not able to quantify the actual oxidative degradation as further breakdown of peroxides usually occurs, therefore simultaneous measurement of secondary products would be appropriate (Barriuso *et al.*, 2013).

Free Fatty Acid Value

FFA are the products of the hydrolysis of oils and fats (Mahesar *et al.*, 2014). Throughout the heating process, the moisture present in the oil samples will induce hydrolysis reaction, which involves the breakage of triglycerides, producing glycerol, di- and mono-acylglycerols, and FFA (Nayak *et al.*, 2016). Hydrolysis occurs more easily in oil containing short and unsaturated fatty acids compared to oil containing long and saturated fatty acids as the water solubility of short and unsaturated fatty acids are higher than long and saturated fatty acids (Choe and Min, 2007).

FFA are also known as pro-oxidants and the effects are subjected to the type of fatty acids (Waraho *et al.*, 2011). The pro-oxidant action of FFA might be due to the presence of carboxylic groups which increase the rate of breakdown of hydroperoxides (Miyashita and Takagi, 1986; Fregaa *et al.*, 1999). FFA determination is relatively rapid and reliable, therefore it is one of the widely used quality indices during food processing, manufacturing, storage and marketing of edible oils (Ali and Abdurrhman, 2013; Ahmad Tarmizi and Ismail, 2007). FFA content is one of the widely used quality indices during manufacturing, storage and marketing of edible oils (Ali and Abdurrhman, 2013). Acid value is used to measure the concentration of FFA in oil. Higher acid value is recorded in oil samples with higher level of FFA, which indicates decreased oil quality (Atinafu and Bedemo, 2011).

***p*-Anisidine Value**

During lipid oxidation, hydroperoxides, the primary oxidation products, breakdown to generate secondary oxidation products (alcohols, aliphatic aldehydes, acids, hydrocarbons and ketones) which have higher stability during the heating process, in control of the off-flavours and off-odours of edible oils. Simultaneous detection of primary and secondary lipid oxidation products is essential to ensure a better monitoring of lipid oxidation process during the heating process. It has been reported that *p*-AV is a reliable measurement of the level of secondary oxidation products (Poiana, 2012). The *p*-AV test evaluates the concentration of aldehydes, predominantly 2-alkenals, exist in the oil. The *p*-AV increased in the soyabean oil samples with the longer of storage time under light, indicating an increase in oxidation level. The reaction between aldehydic compounds in oil samples and *p*-anisidine will lead to an increase in absorbance at 350 nm. The pattern of variations in *p*-AV of the oil samples was comparable to the variations in their *p*-AV (Yildiz *et al.*, 2001).

The generation of secondary oxidation products varies with different types of oil (Kaleem *et al.*, 2015). A study reported that *p*-AV increased more significantly in oil samples undergoing deep-frying process, followed by air-light exposure, and air exposure. Besides, *p*-AV of oil samples increased in the following order: soyabean > corn> olive (Naz *et al.*, 2004). The *p*-AV values also increased due to prolonged storage. According to Mohdaly *et al.* (2010), the *p*-AV of the oil samples reached a maximum value after 72 hr of storage (Mohdaly *et al.*, 2010).

MECHANISMS UNDERLYING LIPID OXIDATION-INDUCED INFLAMMATION

The consumption of oxidised oils may affect the lipid metabolism, which can be detected by the changes in tissue fatty acid composition (Kummerow *et al.*, 2004). Based on a previous study, increased amounts of arachidonic acid (AA) in tissue lipids were detected in animals fed on oxidised oil (Eder, 1999). AA can be converted to eicosanoids that play a significant role in inflammatory processes, such as prostaglandins, thromboxanes, and leukotrienes by cyclooxygenases (COX) and lipoxygenases (LOX) (Patterson *et al.*, 2012; Calder, 2009). Leukotriene B_4 (LTB_4) has many pro-inflammatory roles, such as acting as chemotactic agent for leukocytes, activating neutrophils, accelerating generation of reactive oxygen species (ROS), inducing discharge of lysosomal enzymes, and increasing vascular permeability. The LTB_4 also increases generation of inflammatory cytokines, such as IL-1β, IL-6 and TNF-α by macrophages. The excess production of prostaglandin has a number of pro-inflammatory effects. For instance, prostacyclin (PGI_2) and prostaglandin E2 (PGE_2) play a significant role in the development of arthritis by mediating acute inflammatory response. In addition, PGE_2 can increase its own synthesis via induction of COX-2, followed by increased production of IL-6, a pro-inflammatory cytokine in macrophages (Patterson *et al.*, 2012).

The oxidation of lipids will lead to production of dietary lipid oxidation end products in a substantial amount, which are cytotoxic and genotoxic. Besides, the free radicals generated throughout lipid oxidation may lead to oxidative stress, which activate the nuclear factor κB (NFκB) (Maehre *et al.*, 2015). The NF-kB regulates a number of cytokines (*e.g.*, IL-1, IL-2, IL-6, IL-12, and TNF-α), chemokines (*e.g.*, IL-8, monocyte chemoattractant protein-1), cell adhesion molecules (*e.g.*, sICAM, sVCAM), and inducible effector enzymes (*e.g.*, inducible nitric oxide synthase and COX-2) (Patterson *et al.*, 2012). After the dietary intake of oxidised lipids, several dietary lipid oxidation end products, which are absorbed from the intestine to the circulatory system, may function as injurious chemicals that induce inflammatory response which exert impacts not only to circulatory system but also organs, such as the liver, lung, kidney and the gut itself (Kanner, 2007). The consumption of oxidised lipids will destroy essential fatty acids in body, generating toxic compounds and oxidised polymers (Sadoudi *et al.*, 2013). Dietary oxidised fats may enhance LDL cholesterol modification via their lipid peroxidation products (Eder *et al.*, 2003). For instance, oxidised fatty acids can be absorbed into the intestine, followed by esterification to form complex lipids and integration into lipoproteins (Penumetcha *et al.*, 2000). Dietary oxidised fats have been found to increase the susceptibility of lipoprotein to oxidation (Silaste *et al.*, 2004).

Oxidised low-density lipoprotein (LDL) is a potent inducer for the production of inflammatory molecules. Oxidised LDL may stimulate macrophages, which generates intracellular ROS/reactive nitrogen species (ROS/RNS) by several pathways, such as the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) system, the lipoxygenase/cyclooxygenase system, inducible nitric oxide synthase (iNOS), and mitochondrial respiratory chain. Besides, intracellular ROS produced via stimulation of oxidised LDL can induce a number of pro-inflammatory and pro-apoptotic pathways that are controlled by transcription factors, such as NF-κB, followed by production of pro-inflammatory cytokines that cause oxidative stress by increasing the generation of ROS by macrophages, monocytes, and leukocytes (Straliotto *et al.*, 2013; Patterson *et al.*, 2012). Therefore, oxidised lipids can have an effect on signalling mechanisms, cell proliferation, chemotaxis, and cell survival (apoptosis) (Penumetcha *et al.*, 2000). In a nutshell, the consumption of oxidised oils will lead to intake of a number of by-products which activate several molecular pathways, followed by production of inflammatory molecules, which are known to have promoting effects on tumour growth and therefore increase the risk of cancers.

EVIDENCE ON THE INFLAMMATORY EFFECTS OF OXIDISED LIPIDS

Many studies have been done to examine the effects of oxidised oils on inflammation, which are known to be one of the factors that increase the risk of cancers. In this section, previous studies performed to investigate the inflammatory effects of oxidised oils by using cellular, animal or human models will be discussed.

Cellular or *in vitro* Studies

By-products of lipid oxidation are one of the factors that lead to inflammatory responses. The 2,4-De is one of the by-products of peroxidation of PUFA during storage or heating. In a study performed by Chang *et al.* (2005), an enhanced oxidative stress and production of ROS and a decreased reduced glutathione/oxidised glutathione (GSH/GSSG) ratio were exhibited in cultured human bronchial epithelial cells exposed to 2,4-De for 45 days. Consequently, the enhanced oxidative stress resulted in the release of pro-inflammatory cytokines, such as TNF-α and IL-1β.

In contrast, although fish oil contains eicosapentaneoic acids (EPA), an omega-3 fatty

acid, which are highly polyunsaturated and readily go through auto-oxidation, it has been shown to have beneficial effects in chronic inflammatory diseases (Chaudhary *et al.*, 2004). Compared to unoxidised EPA, oxidised EPA is determined to have more inhibitory effects on pro-inflammatory responses in glomerular endothelial cells, including leukocyte-glomerular endothelial cell interactions, cytokine-induced activation of NF-κB in glomerular endothelial and mesangial cells, as well as cytokine-induced glomerular endothelial and mesangial cells expression of MCP-1 and IL-8. These results have been further supported by Sethi *et al.* (2002) who suggested that the anti-inflammatory effects of oxidised omega-3 fatty acids may be attributed to their characteristics in inhibiting the leukocyte adhesion receptor expression and leukocyte-endothelial interactions. Furthermore, oxidation products including peroxides and aldehydes generated from the oxidative modification of EPA might also be responsible for the anti-inflammatory effects via suppression of endothelium-phagocyte interactions (Sethi *et al.*, 1996).

Animal or *in vivo* Studies

PUFA are greatly susceptible to oxidation, generating potentially deleterious 4-hydroxy-2-alkenals. In a study performed by Awada *et al.* (2012), C57/BL6 mice fed on oxidised *n*-3 PUFA diet which was prepared by continuous shaking to reach the sufficient oxidation level, have been shown to demonstrate an increase in concentration of plasma 4-HHE in parallel with expression of GPx2, a gastrointestinal glutathione peroxidase and phosphorylation of NF-κB, a transcription factor involved in inflammation. Besides, higher concentrations of pro-inflammatory cytokine IL-6 and MCP-1 were observed in mice provided with oxidised *n*-3 PUFA diet. These results indicated that dietary consumption of *n*-3 PUFA leads to an accumulation of 4-HHE in blood after their absorption by intestine, which subsequently induces oxidative stress and inflammation in the upper intestine.

A study done by Hamsi *et al.* (2015), Sprague-Dawley rats were fed on diet added with virgin coconut oils heated once, five times and 10 times at 180°C, and each round of heating lasted for 15 min. There was an increase in the level of plasma inflammatory biomarkers, such as sICAM-1, sVCAM-1, high-sensitivity C-reactive protein (hsCRP) and TXB_2 in the group with five times and 10 times heated oils. These results are further supported by Ng *et al.* (2012), which revealed that Sprague-Dawley rats fed on diet containing 15% (w/w) of repeatedly heated palm oil at 180°C for 10 min, had an increased expression of VCAM-1 .

Besides, in a study done by Sukalingam *et al.* (2016), the levels of catalase (CAT), superoxide dismutase (SOD) and glutathione, which are indicative of oxidative stress were increased in the blood collected from animals fed on diets containing palm oil heated for 5 to 10 times at 180°C for 15 min. Oxidative stress is identified to cause inflammation; therefore, the consumption of repeatedly heated oil may induce inflammatory responses. Jaarin *et al.* (2015) also showed that the consumption of high fat diets added with repeatedly heated palm oil, which the temperature of each round reached 180°C and lasted for 10 min, caused greater extent of inflammation in liver compared to control diet without any oil.

In a study conducted by Aruna *et al.* (2005), the activity of phospholipase A increased significantly in the liver of rats which consumed thermally oxidised oil when compared to the normal control rats. Phospholipase A catalyses the hydrolysis of phospholipids into lysophospholipid and free fatty acids (Gunawardena *et al.*, 2014). Lysophospholipids generated can be converted into platelet-activating factor, a type of potent inflammatory mediator. On the other hand, the free fatty acids mainly generated is AA, which is also the precursor of eicosanoid family of potent inflammatory mediators, such as leukotrienes, lipoxins, prostaglandins and thromboxane (Bradshaw and Dennis, 2009). These results were further supported by Lin *et al.* (2000), which reported that PGE_2 level in mice given diet containing 150 g of oxidised soyabean oil/kg were significantly higher than the mice given diet containing 50 g of soyabean oil/kg. Also, higher level of LTB_2 also produced in group given diet containing 150 g of oxidised soyabean oil/kg, compared to other groups that given diet containing 50 g of soyabean oil/kg, 50 g of oxidised soyabean oil/kg and 150 g soyabean oil/kg respectively. Higher liver cytochrome P450 activity was also observed in mice given 50 g dietary oxidised oil/kg. AA can be oxidatively metabolised by cytochrome P450, consequently enhance the production of inflammatory mediators, such as epoxyeicosatrienoic acids (EET) and hydroxyeicosatetraenoic acids (HETE) (Gross *et al.*, 2005).

Epidemiological and Clinical Studies

In a study done by Birlouez-Aragon *et al.* (2010), human subjects were assigned to two types of diet: standard diet (STD) and steamed diet (STMD), for four weeks to investigate the health risk of food heated under high temperature. Both experimental diets were designed to meet the French dietary demand, which contain equivalent quantities of energy and nutrients (35% of energy from carbohydrates, 15% of energy from proteins, and 32% of energy from fats). STD was cooked by using

conventional methods, including frying, grilling and roasting, as well as comprising industrial food that are commonly being cooked extensively, such as coffee, dry cookies and extruded corn flakes. On the other hand, STMD contained food that were cooked with steam methods and involved minimal process, such as sponge cakes, tea and mildly baked bread. STD group which consumed mainly high temperature cooked foods were shown to have lesser concentrations of major antioxidant vitamins (vitamins C and E), and total and reduced (uniquinol) coenzyme Q10 in the plasma compared to STMD group. The reduced concentration of plasma antioxidant vitamins indicated an enhanced oxidative stress and higher susceptibility of plasma lipids against oxidation after consumption of STD. Besides, STD group was demonstrated to have higher carboxymethyl-lysine (CML) content, which is known to be the indicator of Maillard reaction products (MRP). Increased dietary intake of MRP were known to promote the generation of pro-inflammatory cytokines and therefore play an important role in inflammation (Webster *et al.*, 2005; Kitts *et al.*, 2012). Hence, these findings suggested that the dietary intake of high-heat-treated foods promotes inflammatory responses which are associated with higher risk of diseases, such as type-2 diabetes and cardiovascular diseases in healthy individuals. Even though this study did not specifically identify the effect of dietary fats after exposure to high temperature heating on the aforementioned outcomes, the findings however provide an insight into the detrimental impact of high temperature heating to the nutritional quality of cooked foods.

Besides, advanced glycation end-products (AGE) can be found readily in heat-treated foods. The consumption of dietary AGE, a pro-inflammatory mediator has been shown to increase the level of oxidative stress and inflammatory responses. These findings were supported by the study done by Uribarri *et al.* (2007), which revealed the positive correlation of the intake of dietary AGE and serum levels of hsCRP, an inflammatory marker. This study involved 172 healthy volunteers (70 men and 102 women), comprising 69% Caucasian, 17% Asian, 14% African American. Serum samples obtained from the participants were used to test for two common protein-derived and lipid derived AGE: εN-CML and methylglyoxal (MG). The estimation of daily dietary consumption of AGE was done based on a three-day food records, including the information on cooking techniques. The study demonstrated that the serum level of AGE was positively correlated to the dietary consumption of AGE. Consequently, the increased amount of AGE has been reported to enhance oxidative stress and inflammatory responses, which was indicated by the increasing level of hsCRP. However, data derived from this study does not provide a direct measurement of the effect of oxidised oils on cellular inflammatory responses in human model, which may need further exploration.

CANCER RISK OF OXIDISED LIPID

Based on the molecular mechanisms and evidences from cellular, animal and human models, the oxidised lipids were revealed to have effects on the action of inflammatory cytokines, which were known to have inducing effects on tumour growth (Balkwill and Mantovani, 2001). Many studies have reported that the by-products generated during lipid oxidation will increase the risk of developing cancers, such as lung, breast, colon and liver cancers, which will be further discussed in this section.

Lung Cancer

The generation of products during lipid peroxidation can lead to release of substances which may cause changes in cell growth. Chang *et al.* (2005) demonstrated that 2,4-De, which can be found abundantly in heated oils, can lead to enhanced proliferation of human bronchial epithelial cells (BEAS-2B cells) and release of TNF-α and IL-1β, which play an important role in tumour promotion. These results were supported by Wu and Yen (2004) who demonstrated that 2,4-De which formed during the heating of peanut oil can cause DNA damage in human lung carcinoma (A-549) cells.

Besides, *trans,trans*-2,4-decadienal (*tt*-DDE) is one of the most abundant and toxic aldehydes formed from the heating or oxidation of fatty acids, especially PUFA in cooking oils (Fullana *et al.*, 2004). Wang *et al.* (2010) reported that there was a significant increase in the number of alveolar macrophages in bronchoalveolar lavage fluid (BALF) of mice exposed to *tt*-DDE. Nevertheless, there were also enhanced occurrence of bronchioloalveolar junctions (BAJ) hyperplasia and accumulation of phosphorylated signal transducer and activator of transcription 3 (pSTAT3), a type of pro-carcinogenic factor. These findings indicate that intake of oxidised oils containing *tt*-DDE might increase the risk of lung carcinogenesis.

Breast Cancer

In a case-control study performed by Wang *et al.* (1996), the level of lipid peroxidation-related DNA damage was significantly higher in normal breast tissues of cancer patients compared to non-cancer controls. Therefore, lipid peroxidation may increase the risk of breast cancer as the products of lipid peroxidation can accumulate in human breast tissues. Welsch (1994) also stated that the products formed from the activity of cyclooxygenase on

AA, such as PGE_2 might induce mammary gland tumorigenesis, subsequently increase the risk of breast cancer. Furthermore, Boyd and McGuire (1991) showed that high level of MDA was found in urine of women with mammographic dysplasia compared to normal women. Mammographic dysplasia is associated to higher risk of breast cancer, therefore, it is suggested that lipid peroxidation may increase the risk of getting breast cancer.

Colon Cancer

The primary auto-oxidation products of PUFA have been identified to induce DNA synthesis and ornithine decarboxylase activity in colonic mucosa. Bull *et al.* (1988) showed that auto-oxidation products of PUFA may increase the level of tumorigenesis due to their role in stimulating cell division. Besides, lipid peroxyl radicals produced during the oxidation of PUFA could increase the risk of colon cancer by causing DNA damage (Sawa *et al.*, 1998).

In addition, a study had been conducted by Alghazeer *et al.* (2008) to compare the effects of two oxidised lipids: mackerel oil and methyl linoleate on the proliferation and viability of caco-2 cells, which are human colon epithelial cancer cell line. There was significant decrease in cell viability, augmented thiobarbituric acid reactive substance (TBARS) level and induced apoptosis in cells treated with the both types of oxidised lipids. This result indicated that the oxidised lipids induce oxidation to the lipid membrane, followed by generation of harmful products which lead to damage or death of caco-2 cells.

Furthermore, in a study conducted by Udilovaa *et al.* (2003), lipid hydroperoxides present in heated oils were reported to induce lipid peroxidation of biomembranes and exert strong cytotoxic effects on cultured colon cells. On contrary, these effects were not seen when using untreated oils with low hydroperoxide content. Therefore, dietary consumption of oxidised oils may cause oxidative damage and cell death in colon, which lead to increased risk of colon cancer as a result of regenerative cell proliferation.

Liver Cancer

Based on the study done by Ichinose *et al.* (2004), the consumption of oxidised dietary oils may increase the risk of liver cancer. Benign hepatocellular adenoma was observed in the C3H/HeN male mice fed on three types of oxidised dietary oils: lard, soyabean oil and sardine oil. The mice group fed on oxidised sardine oil exhibited the greatest number of tumour incidence and malignant tumours. Besides, there was an increase in the level of 8-hydroxy-deoxyguanosine (8-OH-dG), a hydroxyl radical which was generated during lipid peroxidation, in the liver of mice fed on oxidised lard and oxidised sardine oils. These results indicate that the accumulation of 8-OH-dG is one of the factors that induce development and progression of liver tumour.

In addition to its adverse effects in causing inflammation, HNE acts as a second messenger of oxidative stress in physiological processes (Csala *et al.*, 2015). HNE was known to interact readily with biomolecules such as nucleic acids and proteins due to its high reactivity. In a study conducted by Marquez-Quinones *et al.* (2010), HNE-protein adducts were observed in hepatocyte cytoplasm before the occurrence of hepatitis and their presence were apparent during hepatitis. The formation of HNE-protein adducts was found to be linked to the expression of gluthathione S-transferase P-form, which particularly associated with malignancy (Tew *et al.*, 2011). These results indicate that the HNE protein-adduct formation might be implicated in the primary stages of hepatocyte cancer initiation.

METHODOLOGICAL CONSIDERATIONS AND STUDY LIMITATIONS

Many studies have been carried out to investigate the pro-inflammatory effects of oxidised oils. However, there are no consistent methods for oxidised oil preparation. The methods of preparation of oxidised oil are listed in *Table 2*. A variety of cooking utensils, such as saucepan, fry pan, wok and electrical fryer that are commonly used to fry or heat food have been used in previous studies (Yen *et al.*, 2010; Fararh *et al.*, 2012; Falade *et al.*, 2015; Falade and Oboh, 2015; Jaarin and Kamisah, 2012; Leong *et al.*, 2008; 2012; Gomez-Alonso *et al.*, 2003; López-Varela *et al.*, 1995; Owu *et al.*, 1998; Farag *et al.*, 2010). When the supply of oxygen is practically unlimited, the rate of oxidation increases when the oil sample has higher ratio of surface to volume (Crapiste *et al.*, 1999). Therefore, the difference in size and shape of the cooking utensils will result in different levels of oxidation albeit other conditions remain constant.

Other than that, there is also a previous study using microwave oven and conventional oven to produce oxidised oil samples (Mahmoud *et al.*, 2009). Microwave oven generates radiation while conventional oven uses a stagnant heat source to heat the oil samples. The effects of microwave heating on the oil samples can differ significantly from those heated using conventional oven and also conventional cooking methods (as mentioned earlier) due to the exposure of microwave energy. A high number of free radicals can be created from microwave energy which might further induce oxidation in lipids, especially PUFA that have

TABLE 2. OXIDISED OIL PREPARATION METHODS

No.	Type of vegetable oil	Type of cooking utensils	Volume (litre)/ weight (kg)	Temperature (°C)/ Power (W)	Duration	Type of food fried using heated oil and duration	Reference
1	Soyabean oil	Iron saucepan (bore of 45 cm and a depth of 20 cm)	7 litres	180 ± 5°C	4 intermittent days, total 22 hr	100 g chicken nuggets (4 min) or sweet potatoes (2 min)	Yen *et al*. (2010)
2	Sunflower oil	Cast iron wok	3 kg	200°C	12 hr and 24 hr	Wheat flour dough sheets (10 x 4.5 x 0.15 cm) for 3 min	Fararh *et al*. (2012)
3	Palm oil	Stainless steel fry-pan	0.25 litres heated oil + 7.50 litres fresh oil	180°C	10, 15 and 20 min	None	Falade *et al*. (2015)
4	Sunflower oil (refined)	Commercial electrical fryer	3 litres (addition of 4.5 litres fresh oil to replace the oil loss during frying)	180°C	20 min	0.5 kg potatoes (2 mm thick) for 8 min	López-Varela *et al*. (1995)
5	Pure Arachis oil	Stainless steel frying pan	0.25 litres	220°C	20 min	None	Falade and Oboh (2015)
6	Refined olive oil and extra virgin olive oil	Pyrex Petri dishes (14 cm diameter) in microwave oven and conventional oven	0.025 ± 0.001kg	500 W (microwave oven), 2 00°C (conventional oven)	3, 6, 9, 12, 15, 20, 25 and 30 min	None	Mahmoud *et al*. (2009)
7	Palm oil or soya oil	Stainless steel wok	2.5 litres	180°C	10 min (5 times heating with cooling interval of ≥ 5 hr)	Sweet potato slices (1 kg)	Jaarin and Kamisah (2012)
8	Refined sunflower, palm and canola oil	Deep fat-dryer	2 litres	180 ± 5°C	5 hr (4 times) per day for 4 days	Potato chips (2, 4, 50 mm)	Farag *et al*. (2010)
9	Palm oil	Stainless steel wok	2.5 litres	180°C	10 min heating with (5 or 10 times cooling interval of 5 hr)	Sweet potato slices (1 kg)	Leong *et al*. (2008; 2012)
10	Extra virgin olive oil and refined olive oil	Deep fryer	2 litres	180°C	10 min (2 operations per day for 6 days)	Potato slices (200 g) (40-50 x 10 x 10 mm)	Gomez-Alonso *et al*. (2003)
11	Palm oil	Stainless steel pot	Not mentioned	150°C	20 min (5 rounds)	None	Owu *et al*. (1998)

weaker double bond which readily accept oxygen to form free radical (Ajayi *et al*., 2014).

The volume of oil samples used in the heating process also varies from 0.25 litres to 7 litres. According to Choe and Min (2006), oxygen and oil samples can react efficiently when the size of oil sample is small or high ratio of surface to volume. Therefore, the difference in the volume of oil samples will result in different degrees of oxidation, consequently producing different amount of oxidation by-products. Based on previous studies listed in *Table 2*, most of the studies heated the oil samples at around 180°C which is the temperature commonly used in frying purposes. In addition, there are also some studies using heated oils to fry food to mimic frying conditions. However,

inconsistent choices of food used in the studies, such as nuggets, sweet potatoes and wheat flour dough might bring about the formation of different levels of oxidation products due to the chemical reactions between the food products and oil samples. Therefore, a standardised and consistent method in preparing oxidised oil samples is needed in generating comparable results with regards to this topic.

Besides, the storage methods of oxidised oils have not been unified. It has been reported that the level of oxidation is affected by the temperature, light, and the presence of oxygen and moisture (Choe and Min, 2007). Therefore, due to the inconsistent methods used, the data obtained from previous research can be hardly compared. The laboratory output of lipid oxidation products is also further complicated by the possible interactions of oxidised oils with the other components in the samples and chemicals used during analysis, and their tendency to undergo further reactions (Dabrowska *et al*., 2015). Therefore, it is always recommended to use at least three different analytical methods to obtain more accurate results.

Furthermore, the study of oxidised oils is hardly to be conducted up to clinical level due to ethical considerations. Therefore, the inflammation-related cancer risk due to consumption of oxidised oil among human can only be studied by correlating their eating habit and health status. However, food survey is not always accurate and reliable. Most of the oxidised oils studies have been conducted using cellular and animal models. However, there are significant differences between the growth of cells in *in vivo* and *in vitro* conditions, for instance, the tumour-promoting effect of oxidised lipids might be significant in *in vitro* condition, but less significant in the human body due to the complexity of human system. Rodent models are the common choice to mimic human biological system. However, the differences in size, tissue development, lifespan and biological system between rodent and human models are still the factors that impede the progress of research in this area.

CONCLUSION

Based on the evidence available, the dietary intake of oxidised oils may enhance the generation of inflammatory molecules, which have been reported to have promoting effects on tumour growth. Hence, the consumption of repeatedly heated oils, which have enhanced level of oxidation, will increase the risk of cancers. However, there is still lack of evidence on the risk of inflammatory-induced cancers due to the consumption of oxidised oils, therefore more studies are warranted to reveal the link between oxidised oils and cancer progression.

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