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REVIEW
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Fucoxanthin: A Promising Phytochemical on Diverse Pharmacological Targets

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Fucoxanthin (FX) is a special carotenoid having an allenic bond in its structure. FX is extracted from a variety of algae and edible seaweeds. It has been proved to contain numerous health benefits and preventive effects against diseases like diabetes, obesity, liver cirrhosis, malignant cancer, etc. Thus, FX can be used as a potent source of both pharmacological and nutritional ingredient to prevent infectious diseases. In this review, we gathered the information regarding the current findings on antimicrobial, antioxidant, anti-inflammatory, skin protective, anti-obesity, antidiabetic, hepatoprotective, and other properties of FX including its bioavailability and stability characteristics. This review aims to assist further biochemical studies in order to develop further pharmaceutical assets and nutritional products in combination with FX and its various metabolites.

Keywords: fucoxanthin, phytochemicals, antimicrobial activity, anticancer activity, anti-inflammatory activity, enzyme inhibition

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INTRODUCTION

Nutrition plays a major role in preventing lifestyle diseases such as obesity, heart diseases, cancer, diabetes, and other long-term diseases (Esselstyn, 2007; Sirtori et al., 2009). Hence, there has been a growing interest in detecting functional and non-toxic elements from foods to treat and maintain different physical illnesses. FX, a marine carotenoid, is one of these effective ingredients. It is about >10% of the approximated total naturally occurring carotenoids (Peng et al., 2011). FX is an orange pigment, present in chloroplasts of macroalgae and microalgae as a major carotenoid (Moreau et al., 2006; Afolayan et al., 2008; Miyata et al., 2009; Mise et al., 2011; Kim SM. et al., 2012; D'Orazio et al., 2012; Dai et al., 2021). R. Willstatter and H. J. Page (Aronoff, 1950) first extracted FX from three marine seaweeds, *Fucus*, *Dictyota*, and *Laminaria*, in 1914 and Englert *et al.* (1990) determined the complete chiral structure of FX. The remarkable pharmacological activities of FX are related to its

TABLE 1 | Sources of FX and their distribution.

Microalgae/ Macroalgae	Name	Distribution	Ref
Brown seaweeds (Macroalgae)	*Alaria crassifolia*	Japan	Airanthi et al. (2011a)
	Ascophyllum nodosum	Europe, East Greenland, North America	Stengel and Dring, (1998)
	Cladosiphon okamuranus	Japan	Mise et al. (2011)
	Cystoseira hakodatensis	Mediterranean, Indian, and Pacific Oceans	Airanthi et al. (2011a), Airanthi et al. (2011b)
	Ecklonia stolonifera	Japan	Jung et al. (2016)
	Eisenia bicyclis	Pacific Ocean waters centered near Japan, South Korea	Airanthi et al. (2011a)
	Fucus serratus	Atlantic coast of Europe from Svalbard to Portugal, Canary Islands, North-east America Iceland, and Faroe Island	Strand et al. (1998)
	Fucus vesiculosus	Europe, Northern Russia, the Baltic Sea, Greenland, Azores, Canary Islands, Morocco, Madeira, Atlantic coast of North America from Ellesmere, Hudson Bay to North Carolina	Zaragozá et al. (2008)
	Hijikia fusiformis	Japan, Korea, and China	Nishino, (1998), Yan et al. (1999)
	Himanthalia elongata	The Baltic Sea, the North Sea, the north east Atlantic Sea	Rajauria et al. (2017)
	Ishige okamurae	Japan	Kil-Nam Kim et al. (2010)
	Kjellmaniella crassifolia	Japan	Airanthi et al. (2011a)
	Laminaria digitata	Greenland, Russia, Iceland, France, England	Haugan and Liaaen-Jensen (1992), Shannon and Abu-Ghannam, (2017)
	Laminaria japonica	China, Japan and Korea	Das et al. (2008), Zhang et al. (2008), Miyata et al. (2009)
	Laminaria ochotensis	China, Japan and Korea	Miyata et al. (2009)
	Laminaria religiosa	Japan	Mori et al. (2004)
	Myagropsis myagroides	Japan	Heo et al. (2010)
	Padina tetrastromatica	Somalia	Sangeetha et al. (2010)
	Petalonia binghamiae	California	Murakami et al. (2002)
	Sargassum fulvellum	Coasts of the eastern and southern sea of Korea	Miyata et al. (2009)
	Sargassum heterophyllum	South Africa	Afolayan et al. (2008)
	Sargassum horneri	Japan and Korea	Airanthi et al. (2011b)
	Sargassum siliquastrum	Japan	Heo et al. (2008)
	Scytosiphon lomentaria	Denmark	Mori et al. (2004)
	Undaria pinnatifida	Japan, Korea, China, Europe, North America, South America and Australasia	Yan et al. (1999), Hosokawa et al. (1999), Ikeda et al. (2003), Hosokawa et al. (2004), Maeda et al. (2005), Sachindra et al. (2007), Asai et al. (2008), Khan et al. (2008b), Liu et al. (2009), Nakazawa et al. (2009), Airanthi et al. (2011b), Okada et al. (2011)
Diatoms (Microalgae)	*Chaetoseros sp.*	North America	Iio et al. (2011a), Iio et al. (2011b)
	Cylindrotheca Closterium	Northern European seas	Rijstenbil, (2003)
	Isochrysis galbana	Coastal; Atlantic	Raposo et al. (2015), Delbrut et al. (2018)
	Nitzschia laevis	Germany, Argentina	Bingbing Guo et al. (2020)
	Odontella aurita	Denmark, Argentina, Brazil, and Paraguay	Moreau et al. (2006)
	Phaeodactylum tricornutum	Both brackish and marine waters worldwide	Nomura et al. (1997)
	Tisochrysis lutea	Worldwide	Mohamadnia et al. (2020)
	Turbinaria triquetra	Tropical marine waters	Mohamadnia et al. (2020)

unique molecular structure. Chemically, FX has a molecular formula of $C_{42}H_{58}O_6$ with a molecular weight of 658.906 g/mol. Its structure is similar to neoxanthin, dinoxanthin, and peridinin and different from other carotenoids like β-carotene and astaxanthin. FX contains an unusual allenic bond, a 5,6-monoepoxide, and nine conjugated double bonds, and some oxygenic functional groups including hydroxyl, epoxy, carbonyl, and carboxyl moieties (Hosokawa et al., 2009; Gundermann and Büchel, 2014). Until now, 43 of the total approximately 700 naturally occurring carotenoids have been found to contain the allene group and in brown seaweeds, and the first isolated allenic carotenoid was FX (Dembitsky and Maoka,

2007; Britton et al., 2008). FX is more functional because of this exceptional allenic bond (Dembitsky and Maoka, 2007). The water solubility of FX is 0.00057 g/L as determined by the ALOGPS tool (Tetko et al., 2005). Heat, light, oxygen, enzymes, unsaturated lipids, and other prooxidant molecules can easily affect the structure and chirality of FX and make it unstable (Zhao et al., 2014). FX breakdown is initiated at 25–60°C temperature in the absence of light and air at pH 4.6. pH 7.4 can diminish the degradation of FX (Zhao et al., 2019). All carotenoids exist in two isomeric configurations, trans or cis, because of the presence of conjugated double bonds in their polyene chains. Although the major isomer of FX is all-trans FX, the increase of extraction temperature can increase the ratio of cis FX (Kawee-Ai et al., 2013; Susanto et al., 2017). Additionally, the cis-form of FX can be enhanced by ultrasonic therapy. Cis FX shows less antioxidant activity than all-trans FX (Nakazawa et al., 2009; Kawee-Ai et al., 2013).

Generally, microalgae have a higher concentration of FX than macroalgae (Kim S. M. et al., 2012). *Chlorophyceae* (Green algae), *Rhodophyceae* (Red algae), and *Phaeophyceae* (Brown algae) are the three major classes of marine algae (Khan et al., 2010). Among them, *Phaeophyceae* usually contain FX, which absorbs blue and green lights and gives them a brownish-olive color. They are mostly found in both cold and temperate oceans worldwide. The sources of FX and its distribution are represented in **Table 1**. Few brown seaweeds containing FX are edible macroalgae in Southeast Asia and certain European nations. Among them, *Undaria* (known as Wakame), *Laminaria* (known as Konbu), and *Hijikia* (known as Hijiki) are the most common seaweeds as a source of food (MacArtain et al., 2007).

In algae, FX forms a light-harvesting system with chlorophyll and significantly contributes to photosynthesis by absorbing light energy as well as protects chlorophyll from the harmful photooxidative effects of bright light (Takaichi, 2011). It transfers more than 60% of the energy to chlorophyll-a in diatoms (Streckaite et al., 2018). FX also establishes biological functions in marine animals. The enhanced immunological activity and ovulation in sea urchins are one of them (Tsushima, 2007; Yang et al., 2021). Humans can easily absorb FX because of its small molecular weight. Additionally, it is nontoxic and exerts several beneficial biological activities in the human body. Like other carotenoids, FX is a potent antioxidant due to its singlet oxygen-quenching functionality (Sachindra et al., 2007; Galasso et al., 2017). It has also received more attention as an anticancer carotenoid. It comprises other numerous pharmacological activities, namely, anti-obesity, anti-inflammatory, antibacterial, antimalarial, antidiabetic, neuroprotective, liver-protective, anti-osteoporosis activities, regulation of intestinal flora, etc. (Krinsky et al., 2004; Kotake-Nara et al., 2005b; Gammone and D'Orazio, 2015; Zorofchian Moghadamtousi et al., 2014). In recent years, FX has been widely investigated for uses in foods, nutraceutical pharmaceuticals, and cosmeceutical industries. Although FX can be produced by chemical synthesis, edible oil extraction from algae is more accessible, safe, and utilizes as FX containing beneficial food without any additional purifications (Miyashita et al., 2020). Industrially, diatoms are the most useful sources because they contain four times more FX than brown seaweeds (Wang et al., 2018). Among all diatoms, *Tisochrysis lutea* provides a higher concentration of FX, and because it does not have a cell wall, it is easy to extract FX from this diatom (Delbrut et al., 2018; Gao et al., 2020; Mohamadnia et al., 2020; Mohamadnia et al., 2021).

Therefore, this article summarizes the present obtainable scientific literatures concerning the metabolism, bioavailability, and health benefits of FX such as its antimicrobial, anti-plasmodial, antioxidant, anti-inflammatory, antiallergic, and anti-obesity effects as well as obesity-related disease prevention including antidiabetic, anti-cardiovascular properties, tumor inhibition, and its protective roles on bones, skin, eyes, and liver.

FUCOXANTHIN METABOLISM

The metabolic fates of FX in humans and other animals indicate that fucoxanthinol (FXol), amarouciaxanthin A, amarouciaxanthin B, halocynthiaxanthin, mytiloxanthin, crasssostreaxanthin A, FXol-3′-sulfate, etc., are some main metabolites of FX. Several investigations were conducted to characterize the metabolic pathway of FX in mice. After oral administration, FX is rapidly deacetylated to FXol by lipase and esterase in the gastrointestinal tract of mice within 2 h. The dietary FX was absorbed in the intestine as FXol, and no pure FX has been found in the plasma or liver tissue of mice (World Health Organization, 1981). In HepG2 cells and in the liver microsomes of ICR mice, further conversion of FXol produced amarouciaxanthin A through dehydrogenation/isomerization (Asai et al., 2004). Amarouciaxanthin A is a marine carotenoid, first found in *Amaroucium pliciferum* (a tunicate) (Matsuno et al., 1985).

FX metabolism is quite different in humans and mice (Hashimoto et al., 2012). An *in vitro* study by Sugawara *et al.* (Sugawara et al., 2002) showed that FX was absorbed as FXol in differentiated Caco-2 cells. The Caco-2 cell is an excellent model for determining the metabolism and absorption of a compound by human intestinal cells (Angelis and Turco, 2011; Hidalgo et al., 2011). Generally, no fatty acid esters of carotenoids are found in human chylomicrons or serum, which also indicates that esters are hydrolyzed in the human small intestine (Khachik et al., 1992; Wingerath et al., 1995; Chitchumroonchokchai and Failla, 2006; Schilter et al., 2010; Wang et al., 2022). Hence, like other carotenoids, dietary FX might be deacetylated by lipase and carboxylesterase in the intestinal tract of humans. NAD^+ works as a cofactor in this process. As no amarouciaxanthin A was founded in plasma, FXol is seemed to be the primary active metabolite in humans. Further biotransformation of FXol to unknown metabolites might be taking place in the human body (Peng et al., 2011; Viera et al., 2018).

BIOAVAILABILITY OF FX

Metabolism, absorption, bioaccessibility, transport, and tissue distribution are some factors that are closely related to the

concept of bioavailability (Fernández-García et al., 2012). Although FX provides promising bioactivities and pharmacological effects, its wider applications in food, cosmetics, and drug industries are limited because of its weak stability (Hii et al., 2010; Zhao et al., 2014; Zhao et al., 2019) and relatively lower bioavailability (Hashimoto et al., 2012). Many researches demonstrated that very few carotenoids like α-carotene and β-carotene are generally consumed in the human small intestine and then transformed into vitamin A (Poor et al., 1993; Oshima et al., 1999; Schweigert et al., 2001). FX is an epoxy-xanthophylls and non-provitamin A-type carotenoid. Although studies reported the metabolism and accumulation of some xanthophylls such as astaxanthin and canthaxanthin (World Health Organization, 1981; Odeberg et al., 2003; During and Harrison, 2004; Showalter et al., 2004; Petri and Lundebye, 2007; Yonekura and Nagao, 2007; Viera et al., 2018), non-provitamin A-type carotenoids (like FX) have insufficient metabolism and bio-accessible information to describe their bioavailability.

The bioavailability of FXol is higher than that of FX; it is lower than other nutritional carotenoids like lutein, β-carotene, and astaxanthin (Viera et al., 2018). There are many hypotheses that might explain the FX's low bioavailability, including the presence of dietary fiber in the algal matrix (Yonekura and Nagao, 2009), a faster first-pass metabolic activity after the intestinal uptake by detoxification enzymes (Asai et al., 2008), or a less affinity of the intestinal transporters because of a lower level of lipophilicity of FX than its metabolic properties (Asai et al., 2008). Besides, the lipophilicity of FX and its metabolites do not influence their tissue distribution, but their higher lipophilicity can decrease depletion (Hashimoto et al., 2012). FX contains a polyunsaturated structure and thus heat and acidic environment can affect its stability (Zhao et al., 2014). Additionally, the degradation of FX can be increased by oxygen, light, and heavy metal exposure during the processing and storage (Pinto et al., 2003; Hii et al., 2010; Sun et al., 2018). Zhao *et al.* (Zhao et al., 2019) reported that pH is the most influential factor on FX stability, followed by temperature and light. According to their results, increasing the temperature from 25 to 60°C substantially increased the FX breakdown. Lowering the pH to 1.2 also mediated FX breakdown, while the degradation was retarded by raising the pH to 7.4 (Zhao et al., 2019).

Because of the low bioaccessibility of FX in humans, different approaches have been developed to increase its absorption, efficiency, and stability. Fish oil and medium-chain triacylglycerols (MCTs) can increase the absorption rate of FX as it is highly soluble in these media (Maeda et al., 2007b; Sachindra et al., 2007). FX, oleic acid (OA), and bovine serum albumin (BSA) can form complexes that can improve the intestinal absorption of FX in water (Liu Y. et al., 2019). Again, the low bioaccessibility of FX can be improved by using encapsulated FX. FX can be encapsulated with biopolymers like maltodextrin (MD), gum arabic (GA), and whey protein isolate (WPI), which improves the thermal stability of FX and intestinal absorption (Sun et al., 2018). Caseinate-stabilized zein particle (zein-Cas)-encapsulated FX also shows efficiently higher bioaccessibility than non-encapsulated FX (Bray et al., 2018). Its dispersibility and bioaccessibility can be enhanced by complete encapsulation within the hydrophilic OA–BSA (oleic acid and bovine serum albumin) particles (Li et al., 2021). So, natural emulsion-based delivery systems with different types of emulsifiers can develop the formation, stability, and bioaccessibility of FX (Ma et al., 2019).

FX AS A MULTI-FUNCTIONAL NUTRIENT IN HEALTH BENEFITS

Antimicrobial Activity

Microbes can easily adapt to new environments, resist old drug treatments, and have a high spreading rate. Nowadays, drug resistance has become a challenging issue for the whole world. For this reason, knowledge concerning microbes has been incredibly increased during the 20th century. Thus, scientists are trying to find newer effective natural antimicrobial agents from bioactive compounds with better potential efficacy against microbes, fewer side effects, better bioavailability than older antibiotics, and minimum toxicity. Carotenoids, especially FX, contain remarkable antimicrobial properties. Thus, FX can be used as a potential inhibitor to prevent various microbial diseases.

Antibacterial Activity

The brown macroalgae extracts inhibit the growth of pathogens more efficiently than the green macroalgae (Lavanya and Veerappan, 2011). FX, the main carotenoid of marine brown seaweed and diatoms, has been reported to show antibiotic properties (Pérez et al., 2016; Shannon and Abu-Ghannam, 2016). FX extracted from *Himanthalia elongate* (Irish brown seaweed) was tested for its potential antimicrobial behaviors against *Listeria monocytogenes* bacteria. The zone of growth inhibition (ZOI) for *Listeria monocytogenes* was 10.89 mm (Rajauria and Abu-Ghannam, 2013). Abou (Abou, 2013) investigated the antibacterial activities of some seaweeds. They extracted FX from *Turbinaria triquetra*, which was recorded to have the highest antibacterial effect against all the selected bacteria including *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Bacillus cereus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa.* The highest activity of FX (100 $\mu g ml^{-1}$) was against *Bacillus subtilis* (ZOI 7.0 mm) (Abou, 2013). Similarly, Karpiński and Adamczak (Karpiński and Adamczak, 2019) observed the antibacterial activities of FX against 20 bacterial species. They found that the mean ZOIs varied from 9.0 to 12.2 mm for Gram-positive bacteria and 7.2–10.2 mm for Gram-negative bacteria. The highest diameter of the inhibition zone was 12.2 mm at a concentration of 62.5 $\mu g ml^{-1}$ FX against *Streptococcus agalactiae.* Zonglin Liu Z. et al. (2019) reported the antibacterial properties of FX isolated from *Undaria pinnatifida* (an edible seaweed) against five human pathogens. According to their *in vitro* study, FX effectively suppressed the growth of *Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Enterococcus sp.,* and *Pseudomonas aeruginosa*. Likewise, several studies have reported that FX shows lower antibacterial effects against Gram-negative bacteria than Gram-positive bacteria (Abou, 2013; Karpiński and Adamczak, 2019). This selective

TABLE 2 | Antibacterial and antifungal activities of FX-containing algae.

Pharmacological effects	Algae species containing FX	Inhibitory activities	Ref
Antibacterial activity	*Himanthalia elongate*	Inhibits the growth of *Listeria monocytogenes* bacteria	Rajauria and Abu-Ghannam, (2013)
	Turbinaria triquetra	Inhibits the growth of *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Bacillus cereus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*	Abou, (2013)
	Undaria pinnatifida	Inhibits the growth of five human pathogens (*Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Enterococcus sp.,* and *Pseudomonas aeruginosa)*	Zonglin Liu et al. (2019)
	Saccharina japonica, Sargassum horneri	Inhibits the growth of *Staphylococcus aureus, Bacillus cereus, Listeria monocytogenes, Escherichia coli*	Sivagnanam et al. (2015)
	Pavlova lutheri, Isochrysis galbana, Navicula sp., Chaetoceros calcitrans, Dunaliella salina, Thalassiosira sp., Chaetoceros gracilis	Inhibits the growth of *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa*	Peraman and Nachimuthu (2019)
Antifungal activity	*Saccharina japonica, Sargassum horneri*	Inhibits the growth of *Candida albicans, Aspergillus brasiliensis*	Sivagnanam et al. (2015)
	Pavlova lutheri, Isochrysis galbana, Navicula sp., Chaetoceros calcitrans, Dunaliella salina, Thalassiosira sp., Chaetoceros gracilis	Inhibits the growth of *Aspergillus brasiliensis, Aspergillus fumigatus, Candida albicans*	Peraman and Nachimuthu, (2019)

antibacterial activity may be influenced by many factors such as charging densities, the lipopolysaccharide (LPS) structure, and different cytoplasmic membrane lipid compositions in Gram-negative and Gram-positive bacteria (Devine and Hancock, 2002). Generally, when an infection is caused by Gram-negative bacteria, FX can help to reduce inflammation. Conversely, FX is ineffective against strict anaerobic bacteria (Karpiński and Adamczak, 2019). The antibacterial activities of FX along with their bacterial inhibition zones are summarized in **Table 2**.

Antifungal and Antiviral Activities

Despite the fact that FX has considerable properties to be as an antifungal agent, there are just a few studies that have investigated it. An *in vitro* study reported that different oil extracts from *Sargassum horneri* and *Saccharina japonica*, which contain FX, exhibited excellent antifungal properties against *Aspergillus brasiliensis* and *Candida albicans*. According to their results, the acetone–methanol mix extract of *Sargassum horneri* shows the highest antimicrobial activity against both fungi (Sivagnanam et al., 2015). Additionally, in a recent *in vitro* study, seven FX containing microalgae (*Pavlova lutheri*, *Isochrysis galbana*, *Navicula sp.*, *Chaetoceros calcitrans*, *Dunaliella salina*, *Thalassiosira sp.,* and *Chaetoceros gracilis*) were screened for their antifungal activities against *Aspergillus fumigatus*, *Aspergillus brasiliensis*, and *Candida albicans*. At MIC: 40 mg/ml, *Dunaliella salina* showed an effective antifungal activity against all the three fungi, with the percentage of growth inhibition of 89.26, 87.67, and 81.02 for *Aspergillus brasiliensis*, *Aspergillus fumigatus,* and *Candida albicans,* respectively. Notably, *Chaetoceros gracilis* extracts also showed excellent inhibitory activity (Peraman and Nachimuthu, 2019). **Table 2** represents the antifungal properties along with the antibacterial activities of FX as well as their inhibition zones.

Additionally, antiviral activities of FX have been appraised in a plenty of experimental studies. An *in vitro* study utilizing Raji cells estimated that at a lower concentration, FX and its metabolites could inhibit 12-O-tetradecanoylphorbol-13-acetate (TPA)-mediated Epstein–Barr virus activation. Among all the metabolites, halocynthiaxanthin (a metabolite of FX in marine animals) shows the strongest inhibitory activity at 500 and 100 M ratios. They showed cytotoxicity at a higher concentration (1000 and/or 500 M ratio per TPA) (Tsushima et al., 1995). Several FX containing seaweeds might be able to reduce the degree of angiotensin-converting enzyme (ACE)/angiotensin II (AngII)/angiotensin receptor II type 1 (ATR1) axis dominance by inhibiting ACE in COVID-19 patients (Tamama, 2020). But the role of FX in this process is still unknown.

Antimalarial and Anthelmintic Activities

Malarial disease is transmitted by mosquitoes and affects humans and other animals (Mordecai et al., 2013; Cowman et al., 2016). It is caused by *Plasmodium* microorganisms and single-celled microorganisms. Among them, *Plasmodium falciparum* is the most common cause of malarial death (Snow et al., 2005; Noor et al., 2014). Even though natural products such as quinine and artemisinin, as well as their synthetic derivatives, have been the backbone of antimalarial chemotherapy for the last 100 years, resistance to these medicines has created the requirement of new treatments to treat the corresponding diseases (Sidhu et al., 2006; Tyagi et al., 2018). Marine compounds can be used to prevent malaria because of their potential biological activities. Afolayan et al. (2008) investigated the antiplasmodial activity of four compounds, sargaquinoic acid, sargaquinal, sargahydroquinoic acid, and FX, which were extracted from the South African algae *Sargassum heterophyllum*. Their results exhibited that FX had the highest antimalarial effect (IC_{50} = 1.5 μg ml^{-1}) against a chloroquine-sensitive strain (D10) of *Plasmodium falciparum.* Although the antiplasmodial effects of FX may be linked to their antioxidant capabilities, further study is required to identify their

TABLE 3 | Antioxidant properties of FX extracted from various algae against free radicals.

Algae species containing FX	Active radicals	Activity	Ref
Hijikia fusiformis *Undaria pinnatifida* *Sargassum* fulvellum	DPPH	Scavenging activity	Yan et al. (1999)
Cladosiphon okamuranus	DPPH	Scavenging activity of FX and FXol extracted with methanol solvent	Mise et al. (2011)
Cystoseria hakodatensis	DPPH, peroxyl radical, ABTS, NO (nitric oxide)	Scavenging activity	Airanthi et al. (2011a)
Sargassum horneri *Eisenia* bicyclis	DPPH, peroxyl radical		
Odontella aurita	DPPH, ABTS DPPH, 12-DS and NB-LP	Scavenging activity of all-trans-FX isomer Reduction activity	Xia et al. (2013) Nishino, (1998)
Undaria pinnatifida	DPPH, ABTS, hydroxyl radical	Radical scavenging and singlet oxygen quenching abilities of FX and its two metabolites (FXol and halocynthiaxanthin)	Sachindra et al. (2007)
Isochrysis galbana	DPPH	Scavenging activity	Mousavi Nadushan and Hosseinzade, (2020)
Sargassum duplicatum	N.D	Inhibitory concentration measurement (IC_{50}) and effect of different extraction methods (ethanol, methanol, and ethyl acetate solvent) on antioxidant activity	Savira et al. (2021)
Phaeodactylum tricornutum	DPPH, hydrogen peroxide, superoxide anion	Reduction activity, effect of different extraction methods (acetone, DMSO, ethanol, and 80% methanol solvent) on antioxidant activity, radical scavenging activity of FX with acetone extract, effect of trans- to cis-form ratio	Kawee-Ai et al. (2013)
Phaeodactylum tricornutum	DPPH	Effect of the different environments (anoxic and aerobic conditions) on scavenging activity, comparison of antioxidant activities with other carotenoids	Nomura et al. (1997)
Sargassum siliquosum *Sargassum polycystum*	DPPH	Trolox equivalent antioxidant capacity, radical scavenging activity, ferric reducing antioxidant power (FRAP), effect of extraction parameters (temperature, time, and solvent to solid ratio)	Lim et al. (2018)
Sargassum fusiforme	DPPH, hydroxyl radical	Effect of blanching treatments (hot water blanching, salt water blanching, microwave blanching, and steam blanching) on scavenging activity	Nie et al. (2021)

mechanism of this action (Afolayan et al., 2008). Peraman and Nachimuthu investigated the anthelmintic activity of FX containing seven microalgae at 20, 40, and 80 mg/ml concentrations against *P. posthuma* (test earthworms). Based on their data, *Isochrysis galbana* and *Chaetoceros gracilis*, containing the highest amount of FX (5.93 and 1.92 mg/g, respectively), exhibited a greater potential anthelmintic activity. Both *Isochrysis galbana* and *Chaetoceros gracilis* showed mortality after 28 min of incubation at 80 mg/ml concentration (Peraman and Nachimuthu, 2019).

Antioxidant Activity

Antioxidants are well-known bioactive chemicals that the human body needs to maintain health (Li et al., 2014; Yadav et al., 2016). They prevent further oxidation reactions from producing free radicals. Free radicals target essential macromolecules leading to cell damage and death and, as a result, cause a variety of serious chronic diseases such as cancer and atherosclerosis (Sailaja Rao et al., 2011; Mittal et al., 2014). A free radical is a molecular intermediate or byproduct of any biological pathway having an atomic unpaired electron. This unpaired electron results in high instability and reactivity of the free radical leading to oxidation or reduction of the biomolecules. Hydroxyl radicals, oxygen singlets, hydrogen peroxides, superoxide anion radicals, hypoclorites, nitric oxide radicals, peroxynitrite radicals, etc., are the frequently found free radicals. Life-leading molecules in the cells such as proteins, carbohydrates, lipids, and DNA or RNA molecules are being degraded by these free radicals (Young and Woodside, 2001; Mohammed et al., 2015). The major sources of the reactive oxygen species (ROS) are mitochondrial respiration, chloroplasts, xanthine oxidoreductase activity, dopamine breakdown, photosensitization reactions, etc. (Turrens, 2003; Berry and Hare, 2004; Moller et al., 2007; Miyazaki and Asanuma, 2008; Gill and Tuteja, 2010; Mohammed et al., 2015). Marine compounds have recently gained the attention of the pharmaceutical and food sectors as a source of potential antioxidants (Ngo et al., 2011). Seaweeds have substantial antioxidant properties that operate in chemical defense mechanisms to survive in harsh marine environments. The antioxidant capacity of brown seaweeds is higher than that of red or green seaweeds, according to many researches on several seaweed species (Jiménez-Escrig et al., 2001; Matanjun et al., 2008; Cox et al., 2010). Many of the biological benefits of marine carotenoids such as anticancer, anti-obesity, and anti-inflammatory effects are linked to their capacity of scavenging ROS (Sachindra et al., 2007; Sachindra et al., 2010). FX is considered to be a useful antioxidant due to its unusual chemical structure, which includes an allenic bond, an epoxide group, and a hydroxyl group (Sangeetha et al., 2009). FX is a potent antioxidant that can quench hydroxyl radicals, superoxide radicals, and singlet oxygen and also prevent oxidative damage caused by H_2O_2 and ultraviolet B radiation (Heo and Jeon, 2009; Sachindra et al., 2010). Its pure form is susceptible to oxidation. Despite this, it was shown to be quite stable in the presence of co-

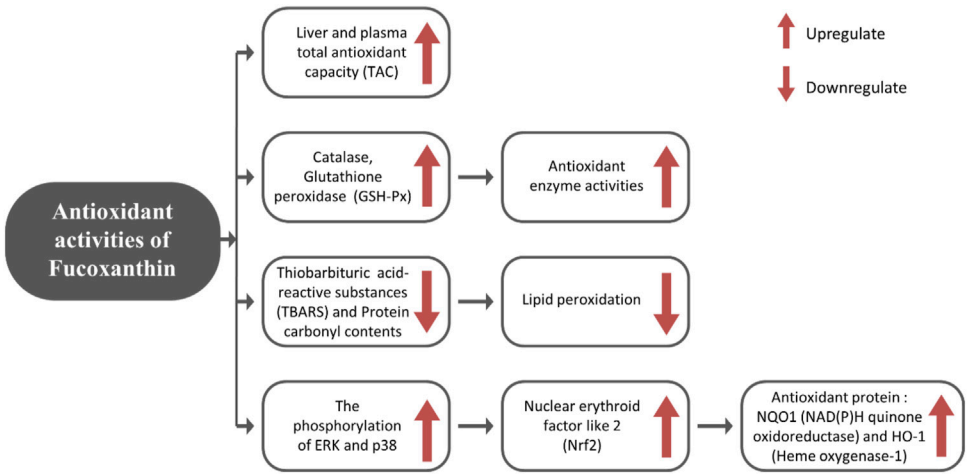

FIGURE 1 | Role of dietary FX in antioxidant activity.

existing antioxidants like polyphenol (Miyashita and Hosokawa, 2007).

The antioxidant effects of FX and its two metabolites (FXol and halocynthiaxanthin) were evaluated *in vitro* concerning singlet oxygen quenching abilities and radical scavenging. FX and FXol had stronger 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity than halocynthiaxanthin. FXol had a higher 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical scavenging activity than FX. Additionally, the antioxidant activity of FX against hydroxyl radical was greater than FXol and halocynthiaxanthin (Sachindra et al., 2007). Trans isomer exhibited stronger activity than cis-isomer. The antioxidant activity of FX against DPPH, hydrogen peroxide, superoxide anion, and reducing power reduced by 21.0, 16.0, 10.3, and 19.7%, respectively, when the percent of cis-isomer increased by 2% (Kawee-Ai et al., 2013). Under anoxic circumstances, FX equimolarly reacted with DPPH, while only one fraction of FX consumed DPPH under aerobic circumstances, and the degree of interaction varied with multiple attempts. Conversely, zeaxanthin, β-cryptoxanthin, β-carotene, lutein, and licopen scarcely reacted with DPPH under anoxic conditions (Nomura et al., 1997). The antioxidant activities of FX extracted from different algae against various active radicals are shown in **Table 3**.

FX exerts its antioxidant impact through increasing antioxidant enzyme activities (catalase, gluthathione peroxidase (GSH-Px)) and total antioxidant capacity (TAC) of plasma, as well as enhancing mRNA expression of nuclear erythroid factor like 2 (Nrf2), which increases the synthesis of antioxidant proteins such as heme oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1) (Liu et al., 2011; Ha et al., 2013). Nrf2 is a key controller of antioxidant protection responses that regulate the rate of essential detoxifying genes (Phase II genes) and antioxidants (Kwak et al., 2001). NQO1 and HO-1 are phase II genes that scavenge reactive nitrogen species (RNS), reactive oxygen species (ROS), xenobiotics, and detoxify electrophiles and also retain cellular reducing capacity (Cho et al., 2002). The antioxidant mechanism induced by FX is described in **Figure 1**.

Anti-Inflammatory/Antiallergic Activity

Inflammation is a part of the complicated protective biological response of body tissues to fight against pathogens, damaged cells, and irritants (Chen et al., 2018). The inflammatory reaction may cause harm to healthy cells, tissues, and organs in the long run by generating superoxide anions, nitric oxide radicals. This may induce DNA damage, tissue death, and internal scarring over time (Jounai et al., 2012). The inflammatory responses are regulated by lipid mediators (prostaglandins and leukotrienes) and cytokines (Ross, 2002). Macrophages produce excessive pro-inflammatory cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and inflammatory mediators such as prostaglandin E2 (PGE_2), nitric oxide (NO), and ROS, generated by activated cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS) (Seon-Jin et al., 2003; Walsh et al., 2005; Yuan et al., 2006). Anti-inflammatory drugs work by decreasing these inflammatory elements and their mRNA expressions (Seon-Jin et al., 2003; Yuan et al., 2006). FX exhibited both anti-inflammatory and antiallergic potential in several *in vivo* and *in vitro* studies.

FX suppressed the inflammatory response of endotoxin-stimulated uveitis (EIU) (Shiratori et al., 2005) and dextran sulfate sodium (DSS)-stimulated colitis (Yang et al., 2020). So, FX can be used to control ulcerative colitis (UC), an inflammatory bowel disease. FX and Fxol can also suppress ear swelling, ear edema, and erythema (Khan et al., 2008a; Khan et al., 2008b; Sakai et al., 2011; Sugiura et al., 2016). This anti-inflammatory effect is comparable with epigallocatechin gallate (EGCG). FX inhibits mast cell degranulation by reducing the antigen-stimulated aggregation of high-affinity immunoglobulin E (IgE) receptors where mast cell degranulation signals activation, which were essential in inflammation and instant allergic responses (Sakai et al., 2009). Namkoong *et al.* investigated the anti-allergic mechanisms of FX fraction extracted from *Eisenia bicyclis* in

an IgE–antigen complex (IgE/2,4-dinitrophenol (DNP)-BSA)-induced RBL-2H3 mast cells. In IgE/DNP-BSA-induced RBL-2H3 cells, they found that FX inhibited the release of β-hexosaminidase, transcriptional activation of nuclear factor kappa B (NF-κB), and phosphorylation of c-Jun N-terminal kinases (JNK) and extracellular regulated kinase (ERK). So, FX may aid in the prevention of allergic disorders including asthma and atopic dermatitis (Namkoong et al., 2012).

Skin Protection

Skin serves as a primary protection against environmental elements, shielding the body from toxic chemicals, physical injury, pathogenic infiltration, and ultraviolet (UV) radiation. Ultraviolet B-ray (UVB) radiation exposure (280–315 nm) is the primary source of ROS and has been linked to a significant acute skin inflammatory response, which is defined by the activation of innate immune cells including macrophages and neutrophils to the dermis and epidermis (Duncan et al., 2009). Overexposure to UV also causes several cutaneous diseases such as laxity, pigmentation, erythema, wrinkling, and skin cancer. Recently, marine biological active compounds are becoming an important element of skincare products owing to their strong antioxidant and anti-inflammatory properties and their low toxicity (Berthon et al., 2017; Brunt and Burgess, 2018).

Keratinocytes are the most common kinds of cells (make about 90%) in the epidermis, the skin's outermost layer. In human keratinocytes (HaCaT), FX enhances the messenger RNA (mRNA) expression and protein levels of glutathione synthetase (GSS), glutamate-cysteine ligase catalytic subunit (GCLC), phosphorylation of Akt (active form), and the nuclear translocation, phosphorylation of Nrf2. Additionally, FX promotes the binding of the antioxidant response element (ARE) sequence to Nrf2. Thus, FX restores glutathione (GSH) level that had been reduced by UVB irradiation (Zheng et al., 2014). FX shows a protective effect against UVB-induced skin photoaging by significantly suppressing UVB-induced matrix metalloproteinase-13 (MMP-13), vascular endothelial growth factor (VEGF) expression, and epidermal hypertrophy and thiobarbituric acid reactive substances (TBARS) in hairless mice (Urikura et al., 2011). FX lessened the mRNA expression of endothelin receptor A, prostaglandin E receptor 1 (EP1), p75 neurotrophin receptor (NTR), tyrosinase-related protein 1 (TYRP1), melanocortin 1 receptor (MC1R), COX-2, and tyrosinase activity. In this way, FX exhibits the inhibition of UVB-induced skin pigmentation and melanogenesis in melanoma (Shimoda et al., 2010). Filaggrin (Flg) promoter activity can be increased by FX. The protective properties of FX against UV-induced sunburn may be due to the production of filaggrin, which promotes the development of a skin barrier (Matsui et al., 2016).

Anti-Obesity Activity

Obesity is a nutritional disorder, characterized by an excessive or abnormal accumulation of fat in the abdomen and viscera (Kopelman, 2000). It is the most common chronic disease, related to many environmental and genetic factors (Ichihara and Yamada, 2008; Durand et al., 2011; Albuquerque et al., 2017). Obesity increases the risk of many other serious diseases such as heart disease, type II diabetes, stroke, high blood pressure, fatty liver disease, gallbladder disease, high cholesterol, coronary atherosclerosis, sleep apnea, infertility, and certain cancers including breast, endometrial, and colon cancers (Matsuzawa et al., 2003; Fabbrini et al., 2010; Lee et al., 2013; Nigro et al., 2014). As a result, obesity control is a significant public health concern, and the development of non-toxic anti-obesity agents is crucial. According to many researches, FX can potentially inhibit obesity. Even a lower dose of FX can effectively decrease body weight (Tsukui et al., 2009; Woo et al., 2009; Jeon et al., 2010; Hu et al., 2012; Koo et al., 2019), body fat accumulation (Maeda et al., 2009; Maeda, 2015; Hitoe and Shimoda, 2017; Koo et al., 2019), and visceral fat-pad weight (Woo et al., 2009; Jeon et al., 2010; Muradian et al., 2015). Additionally, it lowers the size of adipocytes, the weight gain of white adipose tissue (WAT), while increases the weight of brown adipose tissue (BAT) (Maeda et al., 2005; Maeda et al., 2007a; Miyashita, 2009; Hosokawa et al., 2010; Hu et al., 2012; Miyashita, 2014; Maeda et al., 2015; Miyashita and Hosokawa, 2017) in high-fat (HF) diet-induced obese C57BL/6N mice, diabetic/obese KK-Ay mice, and C57BL/6J mice.

Several ways have been found that describe the anti-obesity effects of FX in experimental animals. Among them, *1*) regulation of lipid metabolism and *2*) effect on uncoupling proteins and adipocyte differentiation are thought to be the major anti-obesity mechanisms of FX.

Regulation of Lipid Biosynthesis and Metabolism

Long-term imbalanced diets create a bad impact on lipid metabolism and cause visceral fat accumulation, resulting in obesity. FX affects lipid metabolism-related pathways and lowers the level of free fatty acids. It positively influences fatty acid β-oxidation, sirtuin 1 (Sirt1)/AMP-activated protein kinase (AMPK) pathway, lipolysis, and bile acid synthesis pathway and negatively influences lipogenesis and mevalonate pathway.

FX increases the fatty acid β-oxidation metabolism by enhancing the mRNA expression of β-oxidation-related acyl-CoA oxidase 1 (ACOX1) (Wu et al., 2015; Jia et al., 2016), carnitine palmitoyl-transferase 1(CPT1) (Woo et al., 2010; Chung et al., 2013; Jang and Choung, 2013; Gille et al., 2019), and peroxisome proliferator-activated receptor (PPAR)-alpha (Wu et al., 2014; Chang et al., 2018; Koo et al., 2019). Fatty acids are broken down to produce energy through the β-oxidation process. ACOX1 is a rate-regulating enzyme of the β-oxidation process in peroxisomes and also responsible for the breakdown of very long-chain fatty acids (Vluggens et al., 2010). Additionally, CPT1 plays a crucial role to control β-oxidation in mitochondria by converting acyl-CoA to long-chain acylcarnitine. It is suggested that increasing CPT1 could be used to develop novel obesity-prevention therapies (Schreurs et al., 2010). PPAR-alpha, a major controller of energy homeostasis, regulates the expression of genes involved in β-oxidation (Reddy and Rao, 2006; Cherkaoui-Malki et al., 2012; Ito et al., 2012; Ren et al., 2019). FX supplementation regulates fatty acid synthesis by significantly lowering the tmRNA expression of

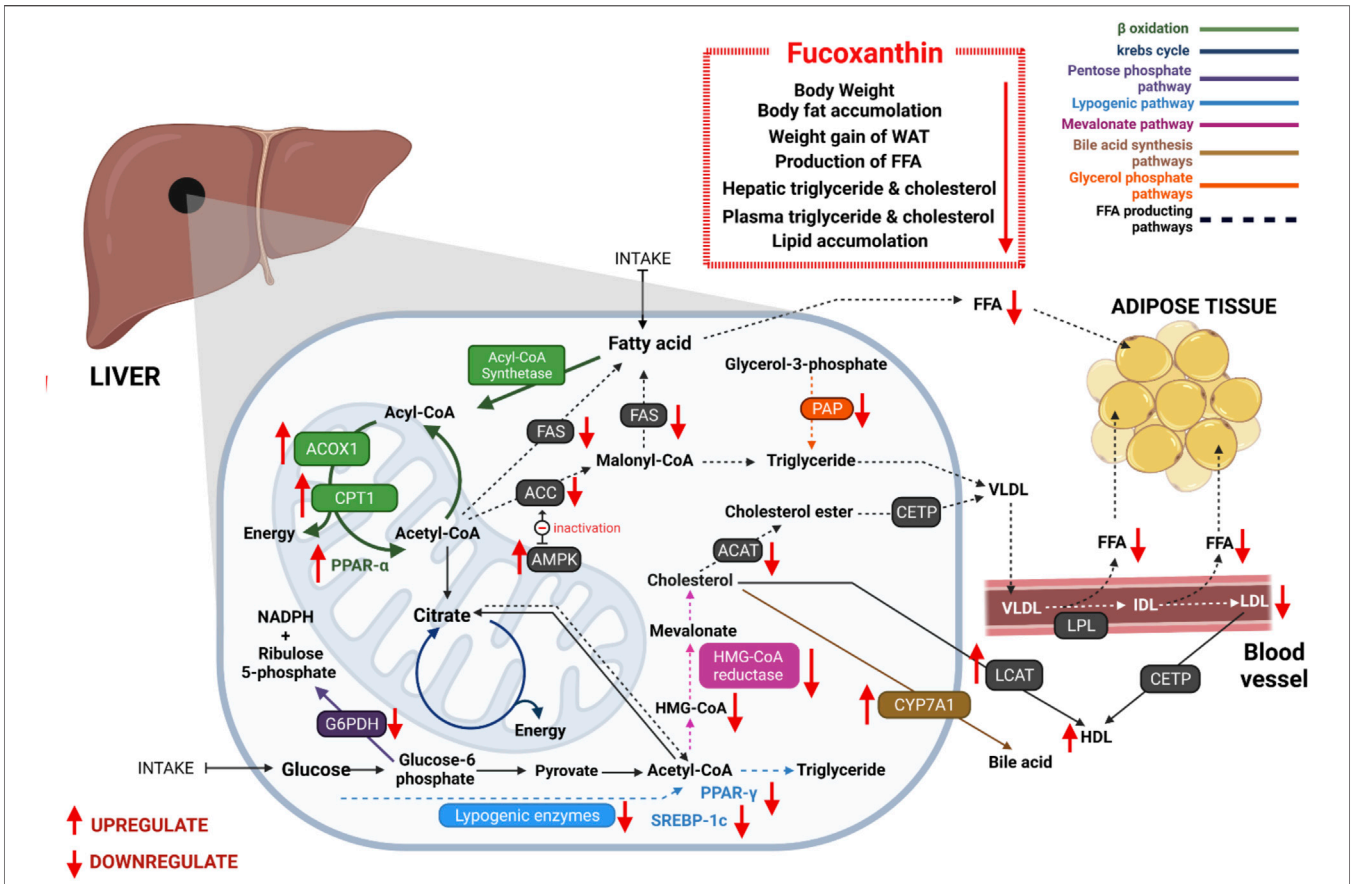

FIGURE 2 | Antiobesity effects of FX through regulating lipid metabolism: FX significantly reduces free fatty acid synthesis *via* controlling many enzymes, which are associated with lipid metabolism. It promotes β-oxidation, bile acid synthesis pathway, and Sirt1/AMPK pathway and inhibits lipogenesis, mevalonate pathway, pentose phosphate pathway, and glycerol phosphate pathway. As a result, plasmatic and hepatic triglyceride and cholesterol concentrations are decreased. It reduces lipid accumulation in hepatic cells and adipose tissues.

acetyl-CoA carboxylase (ACC) (Chung et al., 2013; Grasa-López et al., 2016; Chang et al., 2018) and fatty acid synthase (FAS) (Woo et al., 2009; Woo et al., 2010; Chung et al., 2013). ACC regulates the irreversible chemical reaction of acetyl-CoA to yield malonyl-CoA. This represents a building block for new fatty acid production and inhibits the fatty acid β-oxidation in the mitochondria (Hardie and Pan, 2002; Kim CW. et al., 2010). FAS is an essential enzyme that regulates the conversion of malonyl-CoA and acetyl-CoA to long-chain fatty acids (Park et al., 2019).

All of these findings suggest that FX reduces triglyceride and cholesterol synthesis as well as the production of free fatty acids (FFAs). Thus, the level of hepatic and plasma triglycerides and cholesterol concentrations are decreased and fecal triglycerides and cholesterol concentrations are be increased by dietary FX (Jeon et al., 2010; Woo et al., 2010; Chung et al., 2013). Furthermore, both lymphatic triglyceride absorption and concentration in systemic circulation are reduced by FX and FXol, most likely owing to their inhibitory capacity on lipase activity in the gastrointestinal lumen (Matsumoto et al., 2010). Chang *et al.* (Chang et al., 2018) reported that FX impeded lipid peroxidation and inhibited lipid accumulation in FL83D hepatocytes. The effects of FX on lipid metabolism are shown in **Figure 2**.

Effect on Uncoupling Proteins and Adipocyte Differentiation

According to recent studies, FX processes an anti-obesity activity mostly by stimulating the expression of uncoupling protein-1 (UCP-1) in WAT (Maeda et al., 2005; Miyashita, 2009; Gammone et al., 2014). UCP-1 is a critical molecule for metabolic heat production that is typically expressed exclusively in BAT. Adult individuals, on the other hand, have relatively minimal BAT and most of their fat is accumulated in WAT. Increased UCP-1 expression leads to increased energy expenditure, which helps to prevent excessive fat formation. Regulation of the mRNA expression of UCP-1 in tissues other than BAT by dietary constituents is considered an advanced discovery for effective obesity treatment. FX stimulates thermogenesis by increasing the

level of energy produced as heat in fat tissue. When experimental mice were given *Undaria pinnatifida*, containing FX, UCP-1 protein and its mRNA expression were found in WAT. By boosting UCP-1 expression, 0.2% FX substantially reduced weight growth in mice (Maeda et al., 2005). FX and its metabolites promote UCP-1 in WAT, which causes fatty acid oxidation and heat generation (Kang et al., 2011). FX was also found to promote the β3-adrenergic receptor (Adrb3), which is responsible for thermogenesis and lipolysis. Through the lipolysis pathway, lipid triglycerides are hydrolyzed. This adaptive thermogenesis and lipolysis are seemed to play an important role in limiting weight gain and favoring weight reduction by increasing energy expenditure as heat.

Antidiabetic Activity

FX has promising potential as a therapeutic drug for the treatment of type 2 diabetes and diabetes-related problems. In individuals with type 2 diabetes, glucose production is abnormally elevated. Adipose tissue plays an essential role in fat and glucose metabolism. Adipokines (cell-signaling proteins produced by adipose tissue) affect insulin sensitivity, glucose metabolism in liver, muscle, and adipose tissues. Unbalance WAT causes obesity as well as diabetes mellitus and cardiovascular diseases (Walker et al., 2007). Dietary FX inhibits the formation of WAT in obesity/diabetes mouse KK-Ay (Maeda et al., 2005).

Obesity raises the adipokine tumor necrosis factor-α (TNF-α), which causes the development of insulin resistance as well as diabetes (Nieto-Vazquez et al., 2008; Ye, 2013; Ren et al., 2019). Resistin, leptin, and adiponectin are also associated with insulin resistance (Kitagawa et al., 2004). Maeda *et al.* (Maeda et al., 2007b) reported that FX and fish oil mixture showed a remarkable antidiabetic effect in KK-Ay mice. Both 0.2 and 0.1% FX doses highly decreased plasma glucose and 0.2% FX reduced the plasma insulin level in KK-Ay mice. In addition, the mRNA expression of leptin in WAT and plasma leptin was decreased in the mice fed 0.2% FX and 0.1% FX with fish oil. Although the mRNA expression of tumor necrosis factor alpha (TNF-α) in WAT was remarkably lowered in the mice fed 0.2% FX diet, resistin and adiponectin were not affected by FX. Hepatic gluconeogenic enzyme activities are favorably linked with blood glucose level, while hepatic glucokinase activity is negatively associated (Tirone and Brunicardi, 2001). An excessively high rate of hepatic gluconeogenesis contributes to hyperglycemia in diabetes. FX supplements increased the hepatic glucokinase/glucose-6-phosphatase ratio and glycogen content in diet-induced obese mice (Park et al., 2011). Saturated fat consumption raises the hemoglobin A1c (HbA1c) level (Harding et al., 2001). The HbA1c level is a diabetes and glycemia complication risk indicator (Goldstein et al., 2004). Woo et al. (2010) observed that FX reduced the HbA1c level and blood glucose along with insulin and resistin concentrations in the plasma of HF diet-fed C57BL/6N mice. According to Jung et al. (2012)'s investigation, FX exhibited antidiabetic activity through inhibiting human recombinant aldose reductase (HRAR), rat lens aldose reductase (RLAR), protein tyrosine phosphate 1β (PTP 1β), and advanced glycation end-product (AGE) formation.

Effect on Gut Microbes

Trillions of non-pathogenic symbiotic microbes have been found in the human. In humans, gut microbiota includes the most bacteria species when compared to other regions of the body (Quigley, 2013). Gut microbes aid in the breakdown of various indigestible nutritive compounds, such as cellulose, xylan, and digestion-resistant starch and increase nutrient diet digestion and absorption (Turnbaugh et al., 2006; Rowland et al., 2018). It suggests that nutritive compositions and gut microbes are interrelated and interact with each other. Changes in the group of gut microbes caused by age and other environmental variables (Diet) influence the condition of the host health (Maslowski and Mackay, 2011; Scott et al., 2013). Furthermore, intestinal microbes survive through interacting with their surroundings, which include the central endocrine system, nervous system, and immune system (Cheng et al., 2017; Colpitts et al., 2017; Velmurugan et al., 2017; Yissachar et al., 2017). High cholesterol, high blood sugar, weight gain, and other disorders can be caused by an imbalance of harmful and beneficial microbes in the intestines (Angelakis et al., 2012; Scott et al., 2015; Bo et al., 2017; Jastroch et al., 2020). For this reason, the alteration of gut microbiota by carotenoids has recently become a preferable research focus. Some recent studies show that FX modulates gut microbiota, which can be beneficial for human health.

A significant decrease in beneficial bacteria (such as *Bifidobacterium*, *Lactobacillus*, and butyrate-producing bacteria), as well as an increase in opportunistic pathogenic bacteria (such as Desulfovibrionaceae and Erysipelotrichaceae), can occur, which may cause further inflammation, bacterial and toxin translocations, and obesity (Turnbaugh et al., 2006; Zhang et al., 2010; Qin et al., 2012; Vrieze et al., 2012; Chang et al., 2015; Lecomte et al., 2015; Foster et al., 2016). Sun *et al.* (Sun et al., 2020) reported that FX can alleviate HF diet-induced gut microbiota dysbiosis. According to their 16S rRNA sequencing results, FX can significantly inhibit the growth of Firmicutes phyla (mainly Erysipelotrichaceae and Lachnospiraceae), which is linked with obesity and inflammatory responses (Turnbaugh et al., 2008; Delzenne and Cani, 2011; Remely et al., 2016; Zeng et al., 2016; Lippert et al., 2017; Sun et al., 2020; Zhou et al., 2020). Additionally, FX can increase the growth of *Bifidobacterium*, *Lactobacillus*/*Lactococcus*, and some butyrate-producing bacteria. Sun *et al.*'s (Sun et al., 2020) study also included that 0.05% FX dose with a normal diet enriched the abundance of *Enterococcaceae, Bacteroidetes*, *Bifidobacteriaceae, Ruminococcaceae*, *Bacteroidaes_S24-7_group*, and other strains. In particular, while alleviating HF diet-induced obesity, FX treatment increases *Anaerotruncus, Blautia obeum, Enterococcus durans, Streptococcus, Romboutsia, Lactobacillus equicursoris, Lactobacillus gasseri, Lactobacillus helveticus, Lactococcus lactis, and Lactococcus raffinolactis. Lactobacillus, Bifidobacterium,* and *Bacteroidaes_S24-7_group* inhibit obesity (Delzenne and Cani, 2011; Zhao L. et al., 2017; Shang et al., 2017). *Lactobacillus* can significantly decrease the WAT weight and body weight (Miyoshi et al., 2014; Shirouchi et al., 2016) and is capable of producing large quantities of lactic acid, which enhances gut microbial composition (Damodharan et al.,

2016; Alok et al., 2017). Additionally, *Anaerotruncus*, *Blautia*, *Enterococcus durans*, and some genus in Ruminococcaceae family can possess anti-inflammatory activity, produce butyrate, and improve insulin sensitivity (Wang T. et al., 2012; Broecker et al., 2016; Cook et al., 2016; Kanda et al., 2016; Liu et al., 2018).

Various studies ensure that FX can be used to improve health in many ways by controlling the growth of gut microbes. But the mechanisms of interaction between FX and gut microbes are unknown, and further studies are needed to find out the gut microbe modulation process of FX.

Hepatoprotective Activity

Various studies have determined and showed the optimistic effects of FX on liver protection in rodents including mice, rats as well as in human body environment. Enhancing the oxidation of fatty acids and decreasing the substrates for triacylglycerol synthesis can help in fatty liver diseases (Park et al., 2011). FX has been observed to notably decrease hepatic lipid contents as well as to increase feces weight and fecal lipids due to the inhibition of lipid absorption in C57BL/6N mice administered with HF diet (Woo et al., 2010). The enzymatic reactions associated with hepatic fatty acid synthesis were minimized by FX in liver, reducing the accumulation of hepatic lipid content in HF-fed mice, as described by Park *et al.* (Woo et al., 2010; Park et al., 2011).

Docosahexaenoic acid (DHA), an essential ω-3 functional polyunsaturated fatty acid, stimulates the β-oxidation of hepatic fatty acid in liver as well as minimizes hepatic enzyme activity employed in fatty acid synthesis (Maeda et al., 2008; Woo et al., 2010; Park et al., 2011). FX supplementation effectively reduced the hepatic lipid concentration and plasma triglyceride concentration in C57BL/6N mice (Woo et al., 2010). The activities of G6PD, ME, FAS, and PAP hepatic lysogenic enzymes were inhibited by FX, as found in this study. The contribution of FX and FXol in elevating DHA in KK-A^y mice liver was first described by Tsukui *et al.* (Tsukui et al., 2007). The same contribution of FX was also reported in C57BL/6J mice (Tsukui et al., 2009). In addition, Airanthi *et al.* (Airanthi et al., 2011b) reported the elevation of DHA and arachidonic acid (ARA) in KK-*Ay* mice when served with brown seaweed lipids. In the first study, the small intestinal level of the acid was unchanged. As the enhanced level of ARA (ω-6) has been noticed in FX-fed mice, FX is thought to alter the metabolic pathway of ω-3 and ω-6 fatty acids.

Zheng *et al.* (Zheng et al., 2019) showed the effective role of FX in alcohol-induced liver damage *in vivo*. Its protective effect on the gastric mucosa was also evaluated in this study. Activities of the two enzymes, serum aspartate transaminase (AST) and alanine transaminase (ALT), were lowered by FX treatment, indicating its positive effect on alcohol-induced liver injury (Mohibbullah et al., 2018; Zheng et al., 2019). Fat deposition in alcohol-induced liver was effectively reduced by FX. Immoderate oxidation of hepatocytes due to alcohol intake might also be prevented by FX treatment, improving the antioxidant capacity of the hepatic cells. FX also restricted the pro-inflammatory factor secretion, resulting in lower inflammatory response in alcohol-induced liver injury.

Neuroprotective Activity

Neuronal dysfunction or demission due to central nervous system (CNS) injury induces neuronal apoptosis and degradation. Bioactive natural and synthetic compounds that induce specific mechanisms to protect neuronal cells from incidents occurred by CNS injury are known to have neuroprotective effects (Tucci and Bagetta, 2008; Zarros, 2009). Having several side effects including drowsiness, anxiety, tiredness, dry mouth, etc., synthetic compounds are often postponed by researchers (Narang et al., 2008; Pangestuti and Kim, 2010). Several studies have been conducted to find out the contributions of FX in neuroprotection and revealed significant mechanisms that can help in developing essential pharmaceuticals.

Several studies have revealed the effects of FX in lipopolysaccharide (LPS)-induced RAW 264.7 cells and amyloid beta (Aβ)-induced BV-2 microglia on suppressing the production of NO, ROS, and pro-inflammatory cytokines (Shiratori et al., 2005; Kim N. W. et al., 2010b; Heo et al., 2012; Pangestuti et al., 2013; Choi et al., 2016). A study conducted by Dong Zhao et al. (2017) has proved the dose-dependent activity of FX in LPS-activated BV-2 microglial cells. FX inhibited the protein and mRNA expression of pro-inflammatory mediators involving NF-κB and mitogen-activated protein kinase (MAPK) pathways involving JNK, ERK, and p38 in LPS-activated microglia resembling the finding of previous studies (Shiratori et al., 2005; Kim N. W. et al., 2010b; Pangestuti et al., 2013; Choi et al., 2016). They (Zhao D. et al., 2017) came to a conclusion that FX can be a promising agent arresting neuro-inflammatory diseases and protecting neuronal cells during several CNS injuries.

Ischemic/reperfusion (I/R) injury is considered as the most susceptible disease of brain cells (Lee et al., 2000). FX notably elevated B-cell lymphoma 2 (Bcl-2) expression and alleviated the expression of Bcl-2-associated X protein (Bax). It inhibited caspase-3 in brain tissue and OGD/R-treated neurons (Hu et al., 2018). All these findings suggest a potential role of FX as an anti-apoptotic agent in cerebral I/R injury. Activated Nrf2 possibly protects brain from I/R injury, whereas FX might induce Nrf2 and HO-1 activation, attenuating oxidative stress that is absent from cerebral I/R injury (Zhang et al., 2017; Hu et al., 2018). The overall findings on the FX contribution on neuronal cells define it as a significant neuroprotective agent and a great promise in future therapeutics of neurodegenerative diseases.

Antiangiogenic Activity

Formation of new blood vessels involving migration, growth, and differentiation of endothelial cells is known as the angiogenesis process (Carmeliet, 2003). Angiogenesis is a highly regulated process that occurs in standard physiological activities including embryogenesis, ovary cycling, and wound healing. Rheumatoid arthritis, tumor metastasis, diabetic retinopathy, and several inflammatory diseases are assisted by uncontrolled angiogenesis (Kirk et al., 2004). Prevention of angiogenic abnormality can help defending several diseases as well as pathological emergency conditions. The effects of FX on resisting unwanted angiogenesis have been evaluated by Sugawara *et al.* (Sugawara et al., 2006) in cultured human

TABLE 4 | Inhibitory effect of FX on different cancer types and its underlying mechanism.

Cancer type	Target cell lines	Inhibitory activity	Mechanism	Ref
Lung cancer	A549, H1299, MRC-5	Induces cell cycle arrest, nuclei fragmentation	Upregulates $p21^{waf1/cip1}$, p53, Fas, PUMA, capase-3 or caspase-8 and downregulates Bcl-2	Moreau et al. (2006), Mei et al. (2017)
Liver cancer	HepG2, SK-Hep-1	Induces G0/G1 cell cycle arrest	Downregulates cyclin D	Das et al. (2008), Liu et al. (2009)
Gastric cancer	MGC-803, SGC-7901, BGC-823	Induces cell cycle arrest at S phase and G2/M phase	Upregulates caspase-3 and downregulates Bcl-2, STAT3, cyclinB1	Yu et al. (2011), Yu et al. (2018), Zhu et al. (2018), Xiao et al. (2020)
Breast cancer	MCF-7, MDA-MB-231	Induces apoptosis	Downregulates VEGF-C, VEGFr-3, NF-κB, Akt, P13K, translocates Ca^{2+} from ER to cytoplasm	Hou et al. (2014), Wang et al. (2019)
Leukemia	HL-60, K562, TK6	Inhibits cancer cell proliferation, induces apoptosis	Upregulates caspase-3/7/9, generates ROS, and downregulates Bcl-xL, cleaves PARP	Kotake-Nara et al. (2005c), Kim et al. (2010b), Hosokawa et al. (1999)
Lymphoma	BCBL-1, TY-1	Induces G1 cell cycle arrest and apoptosis	Downregulates NF-κB, AP-1, P13K	Yamamoto et al. (2011)
Glioma	U87, U521, B16-F10	Induces apoptosis	Upregulates caspase-3/9, Bax and downregulates MMP-2, MMP-9, Bcl-2	Nabeshima et al. (2002), Liu et al. (2016b), Chung et al. (2013)
Neuroblastoma	GOTO	Induces G0/G1 cell cycle arrest	Downregulates N-myc	Asai et al. (2004)
Colon cancer	Caco-2, DLD-1, HT-29, WiDr, HCT116	Induces DNA fragmentation, apoptosis, G0/G1 cell cycle arrest	Upregulates p21 and downregulates Bcl -2	Hosokawa et al. (2004), Das et al. (2005)
Cervical cancer	HeLa, SiHa, CaSki	Induces apoptosis	Upregulates Bax and downregulates P13K, Akt, NF-κB, Bcl-2	Jin et al. (2018)
Urinary bladder cancer	EJ-1, T24	Inhibits cell proliferation, induces apoptosis	Upregulates caspase-3, p21 and downregulates CDK-2, CDK-4, cyclin D1, cyclin E	Zhang et al. (2008), Wang et al. (2014)
Prostate cancer	PC-3, DU145, LNCaP	Induces apoptosis, G1 cell cycle arrest	Upregulates caspase-3, Bax and downregulates Bcl-2	Kotake-Nara et al. (2001), Kotake-Nara et al. (2005a), Yoshiko and Hoyoku, (2007)

umbilical vein endothelial cells (HUVECs) and in the rat aortic ring. When a dose of 10 μM FX is applied, significant suppression HUVEC proliferation has been noticed in this study, but FX showed no effect on HUVEC chemotaxis. Differentiation of endothelial progenitor cells into endothelial cells was also significantly suppressed by FX, and the formation of new blood vessel was also restricted. Moreover, FX limited the tube length of endothelial cells. In the experiment on rat aortic ring, the outgrowth of microvessel was effectively suppressed by FX and FXol in *in vivo* and *ex vivo* models of the rat aortic ring. All these findings suggest possible roles of FX in inhibiting or reducing diseases involving the unregulated angiogenesis process.

Anticancer Effects

In 2020, approximately 10 million people died of none other than the second leading cause of death in mankind, cancer (World Health Organization, 2021). It has been known as a deadly disease derived from the uncontrolled cell division of organ tissues and spreads through invasion and subversion of normal tissues (Evan and Vousden, 2001). In the mob of various cancer types, lung cancer, breast cancer, prostate cancer, and colorectal cancer are the most threatening to human in this era (Bray et al., 2018). Poor diagnosis of cancer and low outcomes from conventional chemotherapy indicate the need of new approaches to reduce cancer-induced mortality rate and prevent neoplastic diseases (Sporn and Suh, 2000). Many natural compounds, specially antioxidative compounds such as carotenoids, exhibit anticancer activity and prevent carcinogenesis (Rokkaku et al., 2013; Bolhassani, 2015; Soares Nda et al., 2015; Ávila-Román et al., 2021). FX is now considered to be an effective compound in cancer therapies depending on tumor cell types and stages (Torres et al., 2020). Apoptosis is considered to be one of the six fundamental hallmarks of cancer and is a crucial factor to target for anticancer therapeutics and drugs (Brown and Attardi, 2005). FX is investigated in several cancer models, demonstrating apoptosis and cell-cycle arrest induced by the compound in cancer inhibition (**Table 4**) (Mills et al., 2018). The ability of FX to scavenge free radicals makes it a crucial modulator of carcinogenesis.

Lung Cancer

Inhibition of nasopharyngeal carcinoma cell proliferation by FX is described by Long *et al.* (Long et al., 2020). Non-small-cell lung cancer (NSCLC) is also prevented by FX at a certain dose (Mei et al., 2017). The cell lines of NSCLC, A549, and H1299 were inhibited by this compound. It upregulated $p21^{waf1/cip1}$, p53, Fas, p53 upregulated modulator of apoptosis (PUMA), caspase-3 or caspase-8, and downregulated Bcl-2 in favor to cell-cycle arrest of the tumor cells. Moreau *et al.* (Moreau et al., 2006) showed that FX can trigger apoptosis to A549 and NSCLC-N6 cell lines mediating nuclei fragmentation and formation of apoptotic bodies. Human fetal lung fibroblast MRC-5 was also inhibited by FX (Kotake-Nara et al., 2005b). In a recent study, FX exerted the sensitivity of lung cancer cell lines to Gefitinib (Ming et al., 2021). FX inhibited several pathways and the expression of several proteins including fibronectin, N-cadherin, Snail, Twist, MMP-2, PI3K, p-AKT, and κκB, and increased the TIMP-2 expression resulting in the inhibition of cancer cell migration and invasion in *in vitro* analysis.

Liver Cancer

Liver cancer is considered one of the threatening cancers all over the world. The malignant tumor of liver cancer can be categorized under primary and secondary states. The active role of FX in inhibiting diethylnitrosamine (DEN)-induced liver cancer has been found in rat models (Jin et al., 2019). DEN increases lipid oxidation; hence, inhibiting this compound may reduce carcinogenic processes (Schneider et al., 2012; Ramalingam and Vaiyapuri, 2013; Ding et al., 2017). FX effectively restored normal body weight, liver enzyme concentration, antioxidant enzyme concentration, stress markers, serum albumin, and serum bilirubin in this study (Jin et al., 2019). Das *et al.* (Das et al., 2008) showed that FX-rich fraction (FxRF) from crude methanolic extracts (CMEs) of *C. calcitrans* induced cytotoxicity to liver cancer cell line, HepG2. FX induced the G0/G1 cell-cycle arrest and inhibited the expression of cyclin D; hence, the viability of HepG2 cells was significantly diminished by 25 μM of this carotenoid. The same outcomes were studied by Foo et al. (2019), where cytotoxicity was induced by CME and FxRF to HepG2 cells. Human hepatoma SK-Hep-1 cell proliferation was also inhibited by FX but the compound supported the growth of BNL CL.2 cell, the murine embryonic hepatic cell (Liu et al., 2009).

Gastric Cancer

A study documented the reduction activity of FX on mRNA, myeloid cell leukemia (Mcl-1) expression, and signal transducer and activator of transcription 3 (STAT3) proteins in SGC-7901 and BGC-823 cell lines of human gastric cancer (GC)-inducing cell-cycle arrest in the S phase and mediating apoptosis at the G2/M phase (Yu et al., 2011). In the same study, FX was observed to induce cell-cycle arrest of MGC-803, the human gastric adenocarcinoma cells in the G2/M phase, and also induced apoptosis of the cells. FX reduced CyclinB1 and surviving expression in MGC-803 cells. A further analysis on the reduction of cell viability and proliferation of human gastric adenocarcinoma BGC-823 and SGC-7901 showed the minimizing effect of FX on the corresponding cells (Yu et al., 2018). Mcl-1 is a protein from Bcl-2 family, which induces anti-apoptotic activity. Being a target protein of the TNF-related apoptosis-inducing ligand (TRAIL) signaling pathway, Mcl-1 is a significant target for anticancer drugs (Xiao et al., 2020). STAT3 induces chronic inflammation and acts as a helping factor in tumor generation. Inhibition of these proteins indicated the anticancer role of FX on GC cell lines. FX can be used in gastric adenocarcinoma therapy as it acts safely to the healthy cells. FX downregulated several key proteins including STAT3 and cyclin B1 in MGC-803 cells. FX also induced the G2/M phase apoptosis and cell-cycle arrest in the same study (Yu et al., 2011). In another study, FX upregulated beclin-1 and LC3 expressions, cleaved caspase-3, downregulated Bcl-2 expression, and consequently reduced the cell viability of SGC-7901 cells (Zhu et al., 2018). All these findings prove FX as a significant anti-GC agent.

Breast Cancer

Breast cancer is the most threatening disease to women, which arise from the malignant tumor of the epithelial tissue of the breast. Inhibition of the phenotype of MDA-MB-231 cells, the malignant human breast cancer cell by FX has been demonstrated in a study (Wang et al., 2019). FX significantly reduced tumor-induced lymphangiogenesis in this study. NF-κB, vascular endothelial growth factor (VEGF)-C, VEGFr-3, phosphorylated P13K, and phosphorylated Akt levels are efficiently reduced by FX. *In vivo* and *in vitro* analyses with the MDA-MB-231 breast cancer model showed the reduction effect of FX on microlymphatic vessel density (micro-LVD) in mice and altogether suggests FX to be a potential component of anti-lymphagiogenic drugs applied in anti-malignant treatments of breast cancer patients. Hou et al. (2014) showed the damaging effect of FX on the endoplasmic reticulum (ER) membrane. Translocation of Ca^{2+} from ER to cytoplasm is induced by FX in MCF-7 cells, resulting in apoptosis of the cell. The expression of the SOX9 transcriptional protein is minimized by FX in MDA-MB-231 cells. In combination with adriamycin, oxidative stress-mediated apoptosis was initiated by this compound in breast cancer cells (Vijay et al., 2018).

Leukemia and Lymphoma

Almeida et al. (2018) documented the role of FX in chronic myeloid leukemia (CML), which is the most recurring type of persistent leukemia and is developed by active proliferation of bone marrow hematopoietic stem cells. The authors investigated the FX activity through the *in vitro* analysis of K562 and TK6, the two human leukemia cell lines, at an isolated and a combined form with imatinib (Imat) and doxorubicin (Dox), which are known as anticancer drugs. FX notably inhibited the clonal proliferation of K562 and TK6 and also worked well in combination with imatinib and doxorubicin (Almeida et al., 2018). Investigating the underlying apoptotic mechanism of FX, Kil-Nam Kim et al. (2010a) found that ROS generation, Bcl-xL inactivation, caspase-3 and caspase-7 activation, and poly (ADP-ribose) polymerase (PARP) cleavage were induced by FX, and as a result, apoptotic action toward HL-60 was mediated by this compound. Ishikawa et al. (2008) examined the effect of FX and FXol on adult T-cell leukemia (ATL). ATL is a deadly malignant cancer of T lymphocytes. It develops from the infection of human T-cell leukemia virus type 1 (HTLV-1) and is incurable (Nicot, 2005). In comparison with β-carotene and astaxanthin, FX showed a stronger anti-ALT effect, inducing apoptosis to cancer cells (Ishikawa et al., 2008). Hosokawa et al. (1999) also documented the apoptosis induction of FX on human leukemia cells (HL-60). FX involved caspase-3, caspase-8, and caspase-9 activation to induce apoptotic pathways in cancer cells (Hosokawa et al., 1999).

Among the non-Hodgkin's lymphoma, primary effusion lymphoma (PEL) is a serious cancer derived from the infection of human herpesvirus 8. PEL cell lines including TY-1 and BCBL-1 are suppressed by FX inducing G1 cell-cycle arrest and caspase-dependent apoptosis. FX suppressed the PEL cell growth in xenografted mice, indicating its anti-PEL therapeutic

effect (Yamamoto et al., 2011). These findings indicate that FX can act significantly against leukemia and lymphoma.

Roles in Glioma

Liu et al. (2016b) documented the cytotoxicity of FX to U87 and U521 cell lines, which are known as grade IV glioma or glioblastoma multiforme (GBM) (Rao, 2003; Dunbar and Yachnis, 2010). Despite being the most common primary tumor of CNS, the treatment of glioma including radiotherapy or chemotherapy often fails to reach a favorable outcome. FX inhibited the migration of U87 and U251 cells and their evasion through matrigel membrane as found in *in vitro* analysis by using the scratch wound healing assay and the trans-well assay, respectively (Liu et al., 2016b). For levels of caspase-3, caspase-9, etc., apoptotic proteins are increased by FX. In U87 and U251 cells, the levels of matric metalloproteinases 2 (MMP-2) and MMP-9 were decreased by FX, which proves the crucial role of FX in inhibiting evasion and metastasis of tumor cells (Nabeshima et al., 2002). Moreover, migration and evasion of murine B16-F10 melanoma cells were attenuated by FX, resulting in reduced actin fiber formation and reduced expression of MMP-9 level (Chung et al., 2013). A phosphoinositide 3-kinase (PI3K), Akt, and mammalian target of rapamycin (mTOR) protein inhibit cell apoptosis favoring tumor growth. FX effectively inhibits these anti-apoptotic proteins, increases Bcl-2 associated X (Bax) expression, and decreases Bcl-2 expression and therefore acts as an anti-glioma agent and can be utilized in cancer therapeutics (Liu et al., 2016b).

Colon Cancer

Among the gastrointestinal cancers, colon cancer is the second most frequent. Hosokawa et al. (2004) described the inhibitory activity of FX against the proliferation of human colon cancer cell lines including Caco-2, DLD-1, and HT-29 cells mediating the fragmentation of DNA. This compound remarkably induced apoptosis to the colon cancer cell lines and reduced cell viability at a dose- and time-dependent manner. Interestingly, β-carotene and astaxanthin did not show any adverse effect on Caco-2 cells. FX decreased the level of Bcl-2 proteins, which are anti-apoptotic factors. In another study, several cancer-inducing incidents including colon damage were diminished on the FX treatment (Terasaki et al., 2020). Tumor growth was inhibited, and anoikis pathway was promoted in the carcinogenic mouse model by FX treatment. Moreover, mouse colon carcinogenesis was inhibited by FX that was induced by 1,2-dimethylhydrazine in an *in vivo* study (Kim et al., 1998). Das et al. (2005) observed the anti-proliferative effect of FX on HCT116 and WiDr cell lines, inducing the G0/G1 cell-cycle arrest by upregulating the $p21^{WAF1/Cip1}$, the cyclin-dependent kinase (CDK) inhibitory protein, and retinoblastoma protein (pRb). The initiation crypt foci, known as a preneoplastic colon cancer marker was strongly inhibited in the mice model by FX. In a study, polyp formation was significantly inhibited by FX administration. Moreover, anoikis-like cells of colonic mucosal tissue was upregulated by this compound in mice models treated with azoxymethane and DSS and prevented colorectal tumors (Terasaki et al., 2019). Kotake-Nara et al. (2005b) showed that FX reduced the cell viability of Caco-2 and HCT116 cell lines. Terasaki et al. (2021) investigated the efficacy of FX on azoxymethane or DSS-induced colorectal cancer and found its inhibitory effect in mice on the multiplicity of colorectal adenocarcinoma. FX reduced *Bacteroidlales* and *Rikenellaceae* and increased *Lachnospiraceae,* which indicated a relation between the alteration of gut microbiota and suppression of colorectal cancer in the experimental mice.

Cervical Cancer

The increasing rate of cervical cancer either induced by human papillomavirus (HPV) infection or other factors and its upgoing incidence is threatening the women's physical and mental health. HPV infection is the most common sexually transmitted infection (STI), which transmits through skin-to-skin contact and causes cervical cancer. FX works in combination with the TRAIL pathway and induces apoptosis of HeLa, SiHa, and CaSki, the cervical cancer cell lines by targeting the signaling pathway including P13K, Akt, and NF-κB. FX enhanced Bax expression as well as decreased the Bcl-2 expression in SiHa cell, which induce apoptosis as an outcome (Jin et al., 2018).

Roles in Other Cancers

Bladder cancer is a serious and the most expensive cancer to treat. FX reduces human urinary bladder cancer cell EJ-1 viability and induces apoptosis (Zhang et al., 2008). It inhibits EJ-1 proliferation and causes the increased percentage of hypodiploid cells and DNA ladder and activates caspase-3 activity. Human bladder cancer cell line T24 is also inhibited by FX, as described in a study (Wang et al., 2014). A CDK-inhibitory protein, p21, was increased and CDK-2, CDK-4, cyclin D1, and cyclin E were decreased by FX, as described in this study. Kotake-Nara et al. (2001) and Kotake-Nara et al. (2005a) showed the apoptotic effect of FX on PC-3, DU145, and LNCaP, the prostate cancer cell lines. FX inhibited PC-3 cell line with a 50% inhibitory concentration of 3 μM (Asai et al., 2004). The viability of PC-3, DU145, and LNCaP was minimized to 14.9, 5.0, and 9.8%, respectively, on the FX treatment (Kotake-Nara et al., 2001). FX interestingly reduced the level of Bax and Bcl-2 proteins in PC-3 cells inducing apoptosis in a different way from mechanisms mentioned in other studies (Kotake-Nara et al., 2001; Kotake-Nara et al., 2005a). FX inhibited cell growth of DU145 by inducing the G1 cell-cycle arrest (Yoshiko and Hoyoku, 2007).

Duodenal and skin carcinogenesis in mice was effectively blocked by FX, inducing anti-oxidant activity, cell-cycle arrest, and apoptosis (Liu et al., 2009; Liu et al., 2011; Wang J. et al., 2012). Mouse melanoma cell line B16 was also inhibited by FX (Kotake-Nara et al., 2005b). It prevented duodenal carcinogenesis in N-ethyl-N′-nitro-N-nitrosoguanidine-induced mice (Okuzumi et al., 1993). Moreover, the growth of human neuroblastoma cell line GOTO was inhibited, cell cycle was blocked at the G0/G1 phase, and N-myc gene expression was reduced by FX (Okuzumi et al., 1990). In several cases, FXol, the metabolite of FX (Asai et al., 2004) showed higher anticancer activity and better efficiency in cancer cells including Caco-2 and

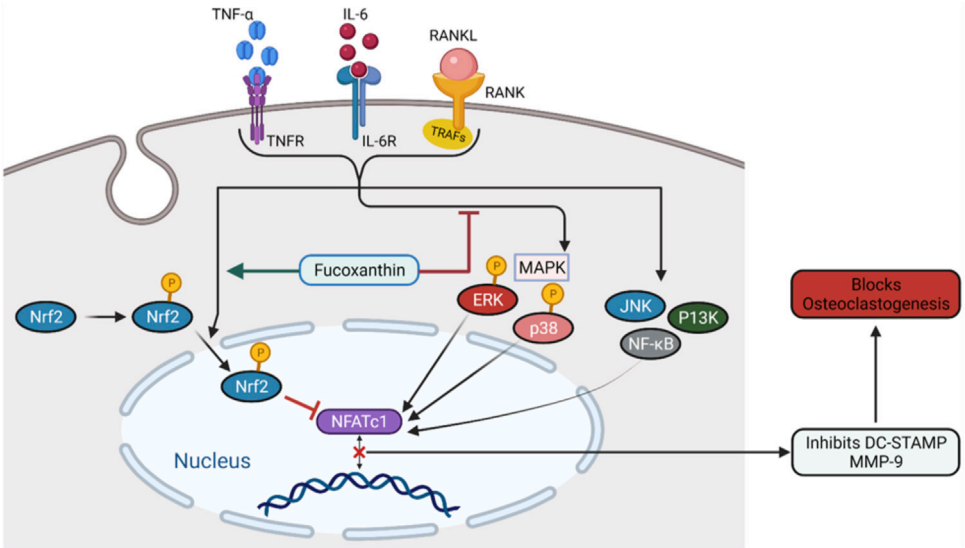

FIGURE 3 | The mechanism of FX inhibiting osteoclastogenesis. FX inhibits ERK and p38, promotes the nuclear translocation of Nrf2, and downregulates NFATc1.

MCF-7 cells. Dietary FX converts to FXol and works in anticancer activities.

Despite a huge number of studies that prove the anticancer/anti-tumor activity of FX, its core mechanisms to induce tumor death are not clearly understood yet (Yoshiko and Hoyoku, 2007). Resting the apoptosis and cell-cycle arrest by FX, this compound may have several other mechanisms, which should figure out in future studies through investigations in different animal models against different types of malignancies.

Bone-Protective Activity

Bone is much susceptible to aging as age-related losses include severe problems such as bone decomposition, bone dysfunction, deterioration of bone structure, etc. (Raisz and Rodan, 2003). Postmenopausal women lack ovarian hormone E2 and elderly women deal with possibilities of osteoporosis (Khosla and Riggs, 2005; Zhang et al., 2011; Jilka, 2013; Khosla, 2013; Tabatabaei-Malazy et al., 2017). Drugs used to treat osteoporosis including bisphosphonate, estrogen, and anti-RANKL antibodies exert many side effects on human body (Wysowski, 2009; Rhee et al., 2012; Khan et al., 2015). Guo L. et al. (2020) studied the roles of FX in ovariectomy-stimulated osteoporosis in female Sprague Dawley (SD) rats. Administration of oral doses of 20 and 40 mg/kg FX for 16 weeks reversed the increase of weight and urine mass due to ovariectomy. Moreover, FX improved the bone mineral content and bone density and therefore provided protection against osteoporosis. In a study investigating medicinal effects of FX on alveolar bone resorption in the ligature-induced periodontitis mouse model, significant reduction of RANKL-positive osteoclasts has been reported (Kose et al., 2016). This result suggests the bone-protective effect of FX against osteoclast-related diseases. Ha et al. (2021) conducted the *in vitro* analysis on soluble receptor activator of NF-κB ligand or tumor necrosis factor-α (TNF- α)/interleukin-6 (IL-6)-stimulated RAW264.7 cell. FX significantly suppressed RAW264.7 differentiation and inhibited bone resorption. It suppressed ERK activation, p38 kinase activation, and initiated nuclear translocation of phospo-Nrf2, as illustrated in **Figure 3**. These findings prove the FX to be a possible therapeutic in the treatment of osteoclastogenesis having no immerse effect on bone formation.

Eye-Protective Activity

Uveitis is a known inflammation of eye, specifically the inflammation of the middle layer of the eye wall tissue, called uvea. Several inflammatory signs including eye redness, foggy vision and pain rise up suddenly, and worsening of the situation can result in severe problems including vision loss (Chang and Wakefield, 2002; Wakefield and Chang, 2005; Bose et al., 2016). Development of lipopolysaccharide-induced uveitis was efficiently suppressed by FX in male Lewis rats, as described in a study by Shiratori et al. (2005). This study reveals the anti-ocular inflammatory activity of FX and can be utilized in future therapeutics. Among the excellent properties of FX, one is that it can absorb spectrum ranging from 350 to 550 nm having 450 nm of maximum absorption peak (Yan et al., 1999; Xiangyong et al., 2014). Between the range of visible light, blue light with a wavelength of 400–500 nm actively damages retinal tissues due to its strong energy and high penetrating power into the cells and organelles (Wenzel et al., 2005; Roehlecke et al., 2009). Liu et al. (2016a) described the function of FX in preventing light-induced retinal damage through *in vitro* and *in vivo* analyses. FX efficiently protected retinal pigment epithelium (RPE) cells from the damaging effect of visible light as per *in vitro*

analysis. Moreover, the *in vivo* analysis described a significant role of FX in preventing retina from photoinduced damage. In these cases, FX showed better result than anthocyanins, lutein, and zeaxanthin, which are known as good ingredients for eye health care (Liu et al., 2016a).

CONCLUSION

Fucoxanthin, a marine carotenoid with multiple disease-preventive qualities, is a crucial element on which a large number of researches are going on. Although the physiological benefits of carotenoids have received less attention, FX has recently gained a lot of interest owing to its significant anticancer and anti-obesity properties. Additionally, it prevents obesity-related diseases such as type 2 diabetics, cardiovascular disease, hepatic diseases, etc. FX exhibits anti-inflammatory and antioxidative effects, and through these activities, it inhibits allergic reactions and UVB irritations. It also shows remarkable organ-protective effects including bone protection, liver protection, neuroprotection, *etc*. Furthermore, several studies have reported antibacterial, antifungal, and antiplasmodial activities of FX. FX can be easily isolated from algae, and has no toxicity but it has lower bioavailability, which can be improved. As we have seen, FX also has a positive impact on gut microbiota; technologies to develop its stability can make it available as an important ingredient of pharmaceutical industries replacing synthetic drugs. Better isolation of fucoxanthin and its systemic modification as well as in-depth experiments can reveal and improve its health benefits in future. Being a non-cytotoxic compound, it can open new directions in therapeutic procedures. If the detailed *in vivo* mechanisms of FX are revealed, the multidimensional use of this carotenoid will be possible with guaranteed biosafety. Despite having huge beneficial effects, it has a few clinical trials on human subjects. Therefore, more studies are needed for a better understanding of FX mechanisms inducing different health benefits in humans and other animals.

AUTHOR CONTRIBUTIONS

MM, AD, and TE conceptualized and designed the article and participated in drafting the article and/or acquisition of data, and/or analysis and interpretation of data; MM, AD, SM, FI, TE, AR, MdK, RD, MP, DC, RS, MaK, AI, and BK prepared the figures and tables. MM, AD, SM, FI, TE, AR, MdK, RD, MP, DC, RS, MaK, AI, and BK wrote, edited, and revised the article critically. RS and TE revised the final written article. All authors critically revised the article concerning intellectual content and approved the final article.

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