Asian Journal of Advances in Research

3(1): 418-439, 2020

ANTICANCER AND IMMUNE-BOOSTING ACTIVITIES OF *Moringa* SPECIES

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AUTHOR'S CONTRIBUTION

The sole author designed, analysed, interpreted and prepared the manuscript.

Received: 08 August 2020
Accepted: 12 October 2020
Published: 30 October 2020

Review Article

ABSTRACT

Cancer is the leading cause of death globally. Imitative drugs are prescribed to patients caused severe adverse effects that caused weakness and losing power of patients. Although many drugs used against several types of cancer, more specific agents with lower side effects are necessary. Natural medicinal plants are used as antitumor and chemo-preventive agents in numerous experimental models of carcinogenesis. *Moringa* tree have shown to be effective against several ailments including cancer which was attributed to its bioactive constituents. These phytochemical compounds proved that they have potential anticancer agents. However, proliferation and the induction of apoptosis are regulated by several mechanisms. The current review will discuss the mechanism by which *Moringa* could fight different types of cancer and its role as an immune-boosting agent.

Keywords: *Moringa*; anticancer activity; immune-boosting activity; mechanism of action.

1. INTRODUCTION

Moringa or drumstick is a member of Moringaceae family [1]. Its parts include the leaves, flowers, pods, seeds, roots, bark and gum [2] as shown in Fig. 1. It has been utilized by the ancient Egyptians, Greeks, Romans, south east and tropical Asian countries, Africa, and Latin America [3]. There are about 13 species of *Moringa*. Many species of *Moringa* that are planted in North-eastern and South-western Africa and Madagascar, contain less quantities of polyphenols compounds in these regions. On the other hand, the Indian species; *M. oleifera* (MO), is being investigated to a large degree. Therefore, the Indian species has been implanted everywhere, specifically in America, Asia, the Pacific, and the Caribbean Islands [4].

Moringa or the miracle tree used as alternative medicine due to its safe characteristics. It contains numerous amounts of vitamin C, protein, fat, β-carotene, iron, potassium, and other nutrients; therefore *Moringa* has been utilized as a substitution nutritional source for supply and growth enhancers in some regions [3]. It was used since long time ago for treatment of many diseases, and it is called a "miracle vegetable" [5]. It is famed as 'mother's preferable friend' in Philippines; because of its utilization to increase woman's milk production and is sometimes prescribed for anemia [6]. Therefore, *Moringa* species were investigated for their various biological activities, including anti-atherosclerotic [7], anti-cardiovascular diseases [8,9], antiviral [10], antioxidant [11] and anticancer effects [12,13]. *Moringa* leaves utilized also for the therapy of many

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diseases such as malaria, typhoid fever, hypertension, diabetes and cancer [14].

The target of this review is to find out *Moringa* mechanism of action for fighting different types of cancer and boosting immune system.

2. *Moringa* BIOACTIVE STRUCTURES

The bioactive phytochemical components of *Moringa* included flavonoids, glucosinolates, phenolic acids, terpenes, alkaloids, and sterols [15].

2.1 Flavonoids

Wang and his colleges [16] reported that flavonoids found in *Moringa* have high antioxidant activity. The main flavonoids of *Moringa* are quercetin, rutin, rhamnetin, isovitexin, kaempferol, apigenin and myricetin [9,17] as represented in Fig. 2.

2.2 Glucosinolate

Moringa contains plentiful of glucosinolates compounds; which of the form of glucosinolate present is 4-*O*-(α-*L*-rhamnopyranosyloxy)-benzyl glucosinolate (4RBGS), niazimicin and niaziminin. There are three isomers of 4RBGS were detected in *M. oleifera* leaf, according to the precocity and physiological characters of the leaves [18]. The cutting or chewing of plant tissues releasing compound named myrosinase which produced isothiocyanates when contact with glucosinolates. The most plentiful isothiocyanate present is 4-[(α-*L*-rhamnosyloxy) benzyl] isothiocyanate, which derived from 4RBGS. Isothiocyanates have many biological activities such as their anti-diabetic, anti-inflammatory, anticancer, and antimicrobial effect which have a major research interest [19,20,21].

2.3 Phenolic Acid

Caffeic acid, gallic acid, ellagic acid, *o*-coumaric acid, ferulic acid, and chlorogenic acid are found in leaf in large quantities; while, syringic acid, gentisic acid, ρ-coumaric acid, and sinapic acid are detected in trace quantities [15,18,22,23]. Tannic acid is a polymer of gallic acid and glucose molecules; that it is water-soluble polyphenols found in MO leave extracts. Due to the presence of different molecular structures for tannic acid it would have been better to speak about tannic acids (in plural). Tannic acid will hydrolyze into glucose and gallic or ellagic acid units [24].

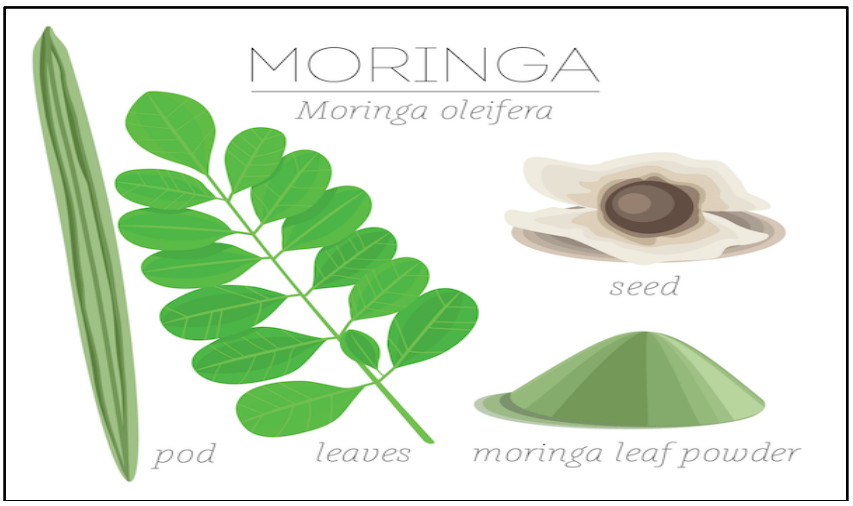
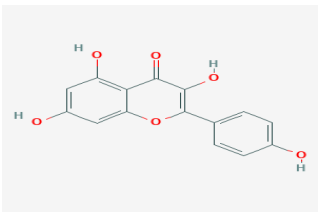
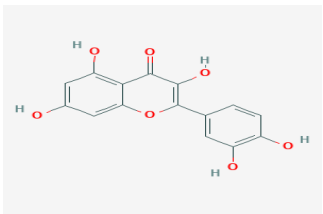


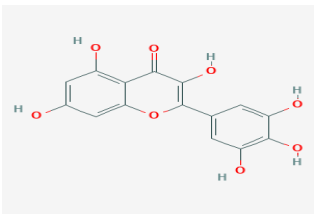
Fig. 1. *Moringa oleifera*, leaves, pod and seeds
https://mysolluna.com/wp-content/uploads/2015/06/unnamed.png



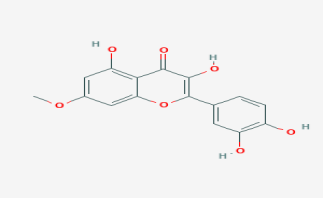
Kaempferol, CID 5280863



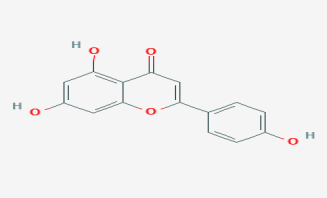
Quercetin, CID 5280343



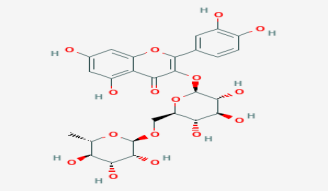
Myricetin, CID 5281672



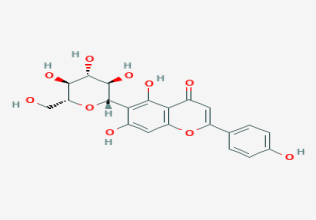
Rhamnetin, CID 5281691



Apigenin, CID 5280443

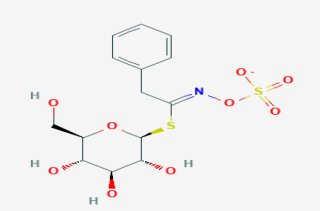


Rutin, CID 5280805

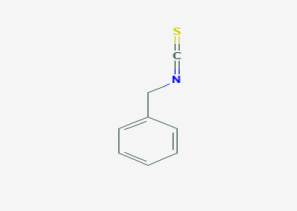


Isovitexin, CID 162350

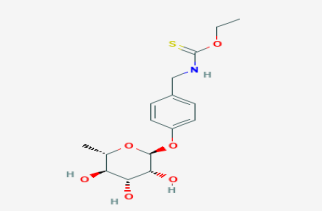
Fig. 2. Chemical structure of flavonoid components extracted from *Moringa*



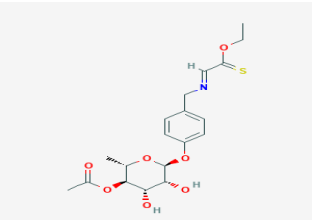
Benzyl Glucosinolate (Compound), CID 21600402



Benzyl isothiocyanate, CID 2346



Niazimicin, CID 10247749



Niaziminin, CID 44559760

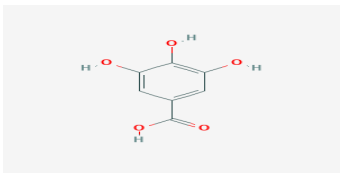
Fig. 3. Chemical formula of glucosinolate components derived from *Moringa*

2.4 Terpenes

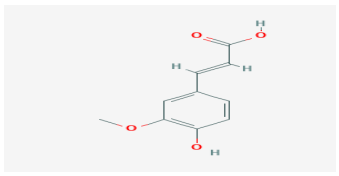
Lutein is the abundant carotenoid found in *M. oleifera* (MO) leaf as reported by Saini and his college [25]. α-carotene which commonly found in other green leafy plants did not found in MO. α-carotenes transformed into lutein. Also, carotenoids such as all-*E*-zeaxanthin, all-*E*-luteoxanthin, 13-*Z*-lutein, and 15-*Z*-β-carotene are separated from MO [25]. On the other hand, β-amyrin, α-amyrin, and lupeol acetate were isolated from *M. peregrina* aerial part [26].

2.5 Alkaloids

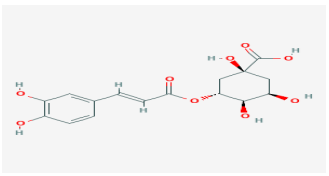
Moringine or myricetin, marumoside A and marumoside B (Fig. 6); and pyrrolemarumine-4″-*O*-α-*L*-rhamnopyranoside were detected in *M. oleifera* leaves and considered as alkaloids compounds [27].



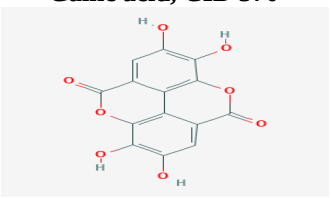
Gallic acid, CID 370



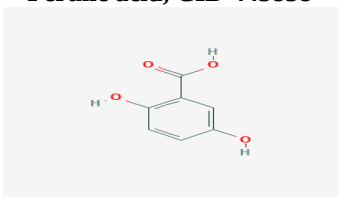
Ferulic acid, CID 445858



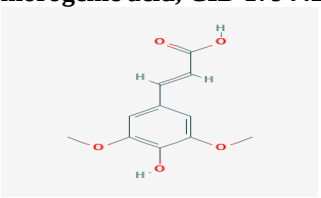
Chlorogenic acid, CID 1794427



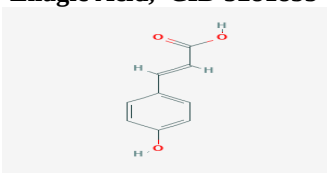
Ellagic Acid, CID 5281855



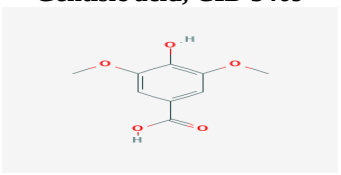
Gentisic acid, CID 3469



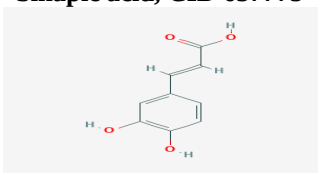
Sinapic acid, CID 637775



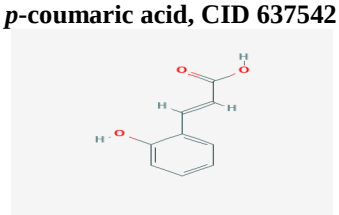
***p*-coumaric acid, CID 637542**



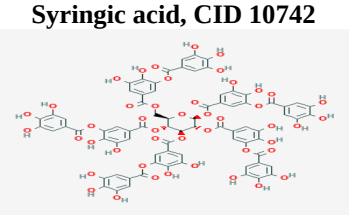
Syringic acid, CID 10742



Caffeic acid, CID 689043

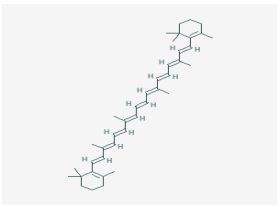


***O*-coumaric acid, CID 637540**

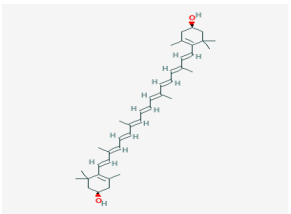


Tannic acid, CID 16129778

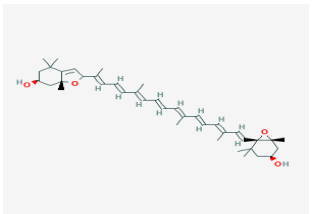
Fig. 4. Chemical formula of phenolic acids extracted from *Moringa*



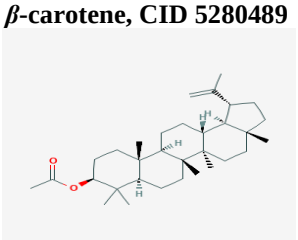
***β*-carotene, CID 5280489**



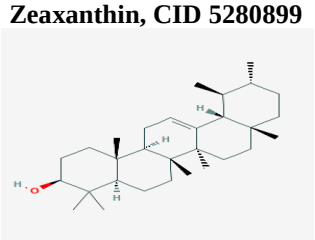
Zeaxanthin, CID 5280899



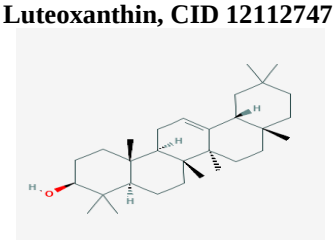
Luteoxanthin, CID 12112747



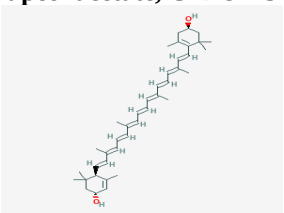
Lupeol acetate, CID 92157



α-amyrin, CID 73170



β-amyrin, CID 73145



Lutein, CID 5281243

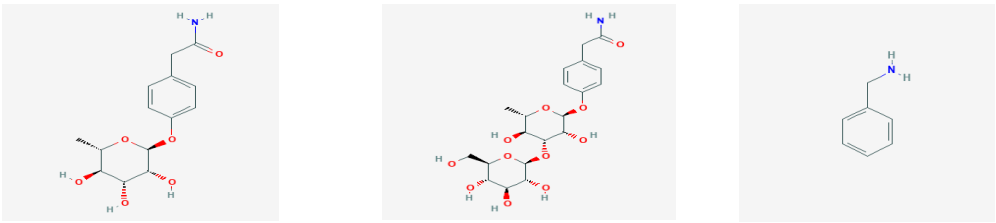
Fig. 5. Chemical formula of some terpenes compounds extracted from *Moringa*

2.6 Sterols

Bargah & Das [28] showed that β-sitosterol-3-*O*-β-*D*-galactopyranoside, which named as a sterol glycosides were separated from MO bark, β-sitosterol was isolated from MO leaf and seed (Fig. 7). Stigmasterol (8.11%), campesterol (23.24%), and β-sitosterol (56.76%) are the major steroidal compounds in *M. peregrina* oil [29]. Another compound named cholest-5-en-3-ol was isolated from *M. stenopetala* root [9,15].

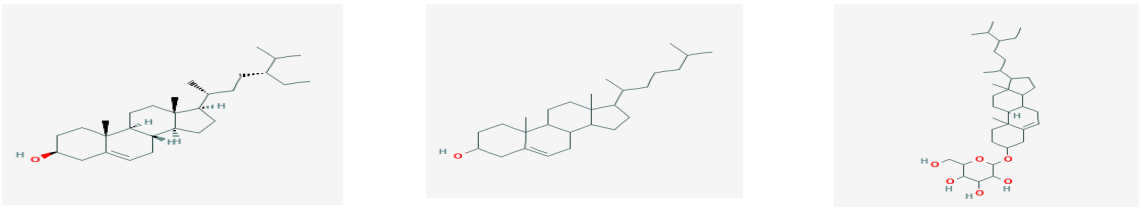
2.7 Amino Acids

The leaves of *Moringa* are wealthy source of tryptophan, cysteine, methionine, and lysine which are essential amino acids [30], and their chemical structures illustrated in Fig. 8.

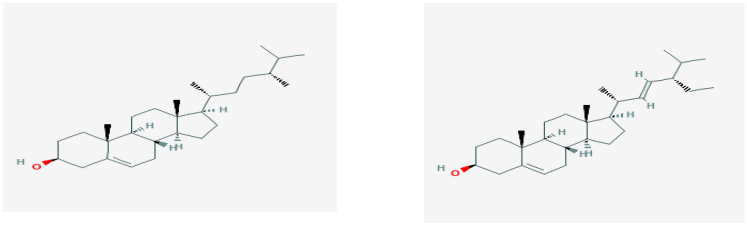


Marumoside A, CID 101794623 **Marumoside B, CID 101794624** **Moringine, CID 7504**

Fig. 6. Chemical formula of some alkaloid components derived from *Moringa*

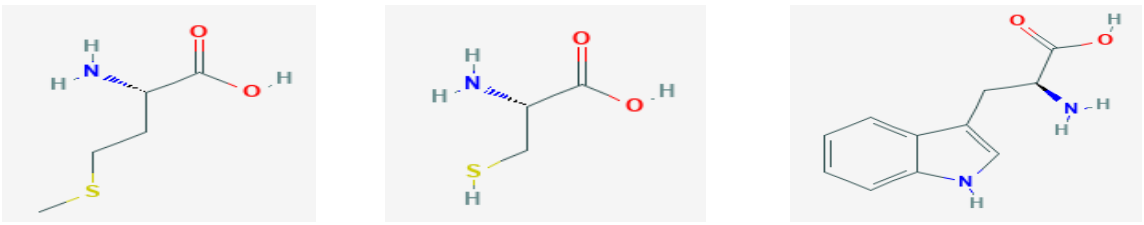


β-sitosterol, CID 222284 **Cholest-5-en-3-ol, CID 304** **β-sitosterol-3-*O*-β-*D*-galactopyranoside, CID 296119**



Campesterol, CID 173183 **Stigmasterol , CID 5280794**

Fig. 7. Chemical formula of some sterol compounds extracted from *Moringa*



Methionine, CID 6137 **Cysteine, CID 5862** **Tryptophan, CID 6305**

Fig. 8. Chemical formula of some amino acids derived from *Moringa*

2.8 Fatty Acids

There are many saturated fatty acids separated from MO seed kernels oil which are linoleic acid (1.27 %), linolenic acid (1.75 %), lauric acid (1.97 %), stearic acid (2.09 %), palmitic acid (12.51 %), as well as oleic acid (74.99 %). The presence of these fatty acids recommends using MO oil in pharmaceutical production preferably as skin creams [31].

3. MECHANISM OF ACTION

Moringa oleifera (MO) leaves are used for medical goals beside human nutrition, because they are wealthy in antioxidants against reactive oxygen species (ROS) and other nutrients, that are generally insufficient in undeveloped countries [30,32]. Many biological effects such as protection against gastric ulcers were reported due to the treatment with MO extracts from seed oils, roots, bark, leaves, and pods [33], and anti-inflammatory effects [34,35]. MO extracts treatment improves renal and functions [36], regulate of thyroid hormone status [37], and reduce hyperglycemia and dyslipidemia [38]. MO leave extracts possess a protective activity against oxidative stress [39], liver damage and hepatic fibrosis [40], hypercholesterolemia [41,42], cancer [39]. The major feature of phytochemicals using as anticancer factors is because they have low side effects.

3.1 Antioxidant Effects

Exogenous antioxidants isolated from natural origins can ameliorate the task of the endogenous antioxidant that is accountable for barring the formation of free radicals [43]. Polyphenols are known as a strong antioxidant, and isolated from MO extracts. Their properties for the neutralizing free radicals by deactivate lipid free radicals, prevent the decay of hydroperoxides into free radicals, and quenching singlet or triplet oxygen [44]. Charoensin and Wongpoomchai [45] reported that MO leaf extract contained polyphenols, flavonoids, and 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) which have scavenging activity [46]. The vitamins (B1, B2, B6, B9, β carotene, A, E, and C) and minerals (K, Ca, Na, Fe, etc.) were also found in MO leaves; that act as a powerful antioxidant. These combination of antioxidants were confirmed to be more efficient than a sole antioxidant, as a result of increased antioxidant cascade mechanisms and synergistic mechanisms [47,48].

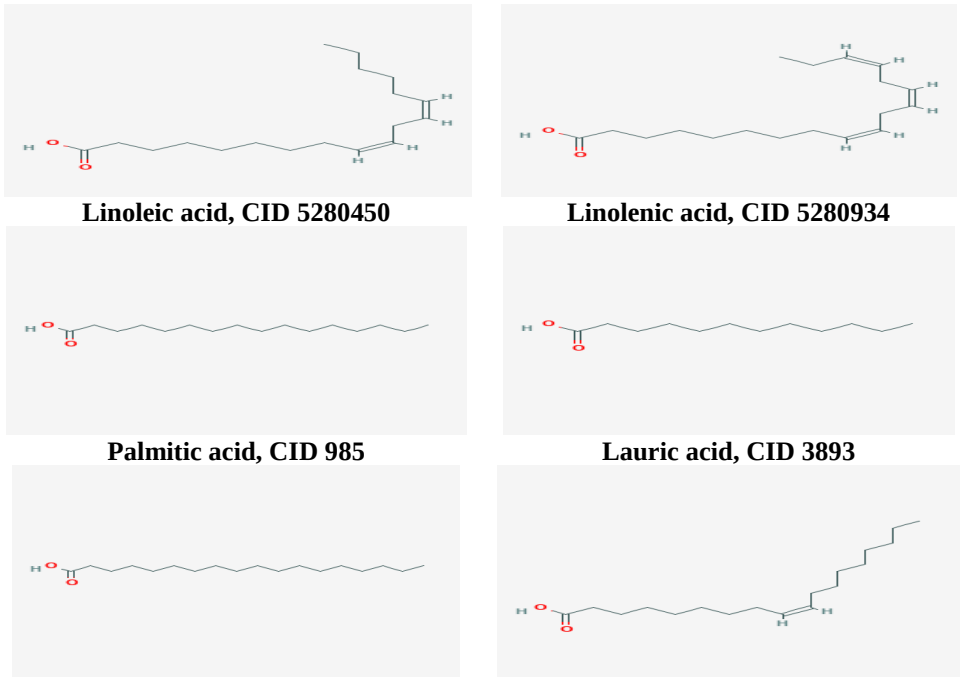


Fig. 9. Chemical formula of some fatty acids derived from *Moringa* kernel oil

The antioxidant and radical scavenging effects of MO leaf extract was delineated by Siddhuraju and his college Becker [49]. The authors showed that leaf extracts decreased linoleic acid peroxidation by 89.7–92.0% beside the scavenging effect on superoxide radicals. To neutralize cell damage promoted by ROS,

living organisms have many anti-oxidative barriers, including non-enzymatic for the most part reduced glutathione (GSH), keepers and these including superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), glutathione S-transferase (GST), and glutathione peroxidase (GPx). GSH has a key role in cancer prevention and oxidative damage neutralization [50]. GPx found in the hepatic cytosol and mitochondria has a detoxification role against H_2O_2; while GST found in the cytosol only and play a major role in xenobiotics discharge and detoxification via GSH [51]. There another cell reinforcement component such as SOD and CAT, which have a key role in cancer prevention. SOD provides cellular protection by catalyzes the dismutation of $O2^-$ to H_2O_2 and O_2; while CAT converting H_2O_2 to H_2O, yielding reliance against ROS [52]. Another investigation by Michotte and his colleges [53], who delineated that myricetin separated from MO seeds has powerful antioxidant activity as compared with α-tocopherol and butylated hydroxytoluene (BHT) which is a chemical lab-made added to foods as a preservative and also used as medicine.

3.2 Immunomodulatory and Anti-Inflammatory Effects

Treatment with MO leaf extract decreased human macrophage cytokine production such as tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6) and IL-8, that induced by cigarette smoke and lipopolysaccharide (LPS) as showed by Kooltheat et al. [54]. Further, Waterman et al. [55] reported that MO alone or its component isothiocyanates inhibited the gene expression and production of inflammatory markers in RAW macrophage cells; RAW 264.7 cells are a macrophage-like, Abelson leukemia virus transformed cell line; and used as a model for the study of cellular responses to microbe. Cyclophosphamide-induced immune-deficient mice treated with MO leaf extract showed activation in both cellular and humoral immune responses, via the augmentation of neutrophils and serum immunoglobulins [56]. Quercetin is a component isolated from *Moringa* concerned with the inhibition of the inflammatory through decreasing the action of NF-kβ (neutral factor kappa-beta). Another mechanism that decreasing inflammation by *Moringa* delineated via the inhibition of mRNA levels of inflammatory cytokines and reductions in endoplasmic reticulum stress in C57BL/6 mice fed the fermented MO for 10 weeks [57]. Phenolic glycoside, 4-[(2′-O-acetyl-α-Lrhamnosyloxy) benzyl] isothiocyanate administration reported to decline inducible nitric oxide synthase (iNOS) levels and cyclooxygenase-2 (COX-2), which proved its potency as an anti-inflammatory factor [19].

3.3 Anticancer Effects

The leading cause of mortality worldwide is cancer; many types of cancer are caused as a result of pollution, overusing of agricultural pesticides, alcohol abuse, and smoking. WHO [58] reported that one death from six cases worldwide is as a result of cancer. Free radicals are these agents that their presence in the body is responsible for DNA damage, which elicits cancer initiation [43]. Leaf extract blocked figuration of cyclophosphamide-micronucleus and mutation of DNA in mice [59]. Chadamas et al. [60] reported the MO could suppress colon carcinogenesis that induce in mice by azoxymethane [61], pancreatic and breast cancer cells [62]. Leaf extract from *Moringa* possess anti-proliferative activity, that induces apoptosis capacity in (KB) tumor cell line [63], and activates the destruction of chemotherapeutic agents in pancreatic cancer cell lines [64], inhibited the growth of several human cancer cells [65]. Extracts from MO leaves have the ability to conserve cells and organisms from oxidative DNA damage, which responsible for cancer and degenerative diseases. Khalafalla, et al. [62] explored that MO leaf extract could decrease the viability of hepatocellular carcinoma, acute lymphoblastic leukemia, and acute myeloid leukemia. β-sitosterol-3-*O*-β-D-glucopyranoside, 4-(α-L-rhamnosyloxy) benzyl isothiocyanate, and niazimicin which are bioactive compounds separated from MO, are responsible for *Moringa* anti-cancer properties [66]. Aja et al. [67] separated 16 organosulfur compounds from MO leaves and 5 compounds from MO seeds, which are responsible for *Moringa* medicinal and anti-cancer properties in an *in vivo* model. Isothiocynate, an organosulfur compound isolated from MO bark found to possess anti-cancer properties. Palmitic acid (Hexadecanoic acid) which is present in all parts of *Moringa* (seeds, bark & leaves) found to have anti-tumor activity in mice as well as eclectic cytotoxicity against human leukemic cells [68]. Previous studies also showed that eugenol (found in bark of *Moringa*) has a strong anticancer potential against gastric cancer [69].

Each type of cancers has its own mutational signature [70]. There are definite genes reliable for cell cycle and death alteration in cancer cells, which differ according to the different types of cancer [71].

The mechanism responsible for cancer cell death and normal cell proliferation can be differed according to the type of cancer. This review will discuss the molecular mechanism by which the *Moringa* species administration could amends cancer cell death (apoptosis) and cell cycle (proliferation) in different types of cancer.

3.3.1 Colon cancer

Colon cancer is a kind that starts in the large intestine. Colorectal cancer is another synonym for colon cancer which is a term that merges rectal cancer and colon cancer that starts in the rectum. It is the 3rd lethal cancer worldwide that affected both males and females [72].

Reda et al. [73] reported that MO was cytotoxic to HCT116, HCT116P53-/-, and Caco2 cancer cell lines, by induced a loss of the integrity of the plasma membrane due to reactive oxygen species produced and indicated an increase in Pre-G0 phase in the three cell lines HCT116, HCT116P53-/- and Caco2 after 6 h treatment, reaching significant levels at 24 h.. Lactate dehydrogenase (LDH) release and ROS production were both time- and dose-dependent in all three cell lines used. LDH is a cytosolic enzyme which oxidizes l-lactate to pyruvate. LDH released or leaked from cytoplasm to the medium indicates changes in the permeability of the plasma membrane and/or incidence of apoptosis or necrosis [74]. Studies on water and ethanolic extracts of MO (especially seeds and leaves) have identified different isothiocyanates (ITCs) with potent anti-cancerous effect [19]. ITCs promote apoptosis, cell cycle arrest, and prevention of metastasis. An early increase in ROS production leads to genotoxic damage that may lead to apoptosis or necrosis. Apoptosis is programmed cell death type I; that plays an important role in maintaining cellular function in various tissues and organs [75].

Al-Asmari et al. [76] reported the cytotoxic effect of MO leaf and bark against HCT-8 cancer cell lines, which showed remarkable anti-cancer properties. Cancer cell survival was significantly minimized; striking inhibition reached to 90% in colony formation, decrease in cancer cell motility as well as increase in the apoptotic cell numbers. MO extracts strongly stop the cell development at the gap2/ mitosis (G2/M) phase (about 2–3 fold) due to its content of anti-cancer compounds, namely D-allose, isopropyl isothiocynate, hexadeconoic acid ethyl ester, and eugenol. Again; MO treatment caused a decrease in the phosphorylation of focal adhesion kinase (p-FAK) and inhibition expression of PI3K/AKT pathway targeting proteins, which plays a significant role in cell invasion and migration [12]. There is another evidence that D-allose present *Moringa* leaf extract declined cancer cell growth at G1 phase (G1- cell cycle arrest) via a specific thioredoxin interacting protein (TXNIP) induction and followed by p27kip1 protein settlement but not affecting the normal cells [77].

Administration of MO methanol seed extract (100 and 200 mg/kg) modulated the macro-and microscopic picture, decreased the ulcerative index, lesion score, oxidative markers myeloperoxidase (MPO) and malondialdehyde (MDA) and inflammatory mediators; nitric oxide (NO), iNOS, tumor-necrosis factor- α (TNF-α), prostaglandin E_2, inhibited the inflammatory enzymes (COX-1 and COX-2), and reduced PCNA index in colonic tissue of treated rats as compared to acetic acid model of experimental colitis in rats in a dose-dependently manner. MDA is a product of degradation by ROS of polyunsaturated lipids [78]; that caused toxic effects in the cells [79]. COX-2, plays a key role in prostaglandin biosynthesis and hence protects colonic mucosa against acetic acid-induced damage [17,62].

TNF-α is a signaling protein called cytokine that involved in systemic inflammation and make up the acute phase reaction. It is produced by activated eosinophils, lymphocytes, neutrophils, macrophages, mast cells, and neurons [80], and released as a result of an inflammatory stimulus (e.g. lipopolysaccharide) as reported by Walsh et al. [81]. Pro-inflammatory mediators, such as cytokines and NO are released by inflammatory cells massively infiltrating the inflamed intestine of patients with inflammatory bowel disease (IBD) as mentioned by Abraham & Medzhitov [82]. Acetic acid produced a dramatic increase in TNF-α, NO, and MDA which are evident in IBD disease. The decreased pro-inflammatory mediators and improvement of macro- and microscopic picture reported in this study proved the strong antioxidant and anti- inflammatory effect of MO [83].

MO leaf methanol extract proved an anti-proliferative role in colon cell line (HCT 116) by an inhibition in the extracellular signal-regulated kinase (ERK) 1/2 phosphorylation, which correlated with metastasis and advancement of cancer [84].

Guon and Chung [85] delineated that treatment of MO (150 μg/mL) changed the ratio of apoptotic cells increased from 8.3% in control to 40.9% in HCT 116 cell line. This data suggesting that the apoptosis took place due to the conversion of mitochondrial pathways signaling, via the stimulation of caspases 3 and 9 (Caspases are family of calcium-dependent cysteine proteases) joined by Bcl-2 inhibition.

3.3.2 Liver cancer

Liver cancer is cancer that begins in the liver. Several types of cancer can form in the liver. The most common type of liver cancer is hepatocellular carcinoma (HCC), which begins in the hepatocytes and occurs most often in people with chronic liver

diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection [86].

MO (500 mg/kg) for 1 week exhibits antitumor, antioxidant and hepato-protective properties in rats; as delineated by Sadek et al. [87], who assessed that the chemo-preventive proficiency of MO against diethyl nitrosamine (DEN) at a dose level 10 mg/kg for 16 weeks. DEN is a carcinogenic organic compound that activating oxidative damage and causing HCC.

The treatment with MO blocked oxidative damage by 46.8%, and diminished 8-hydroxy-2-deoxyguanosine (8-OHdG) levels by 29%; which created by ROS causing the maturation cancer cells. MO clearly diminished β-arrestin-2, B-cell lymphoma 2 (Bcl-2) expression and B-cell lymphoma-extra-large (Bcl-xl) with increased of Bax and caspase-3 expressions, and decreased the Bcl-2/Bax ratios compared with the DEN group. Bcl-2 family; is a family of anti-apoptotic markers, act via the neutralization of the pro-apoptotic markers like Bax and suppose a crucial role in causing the cancer cells to endure apoptosis [88,89]. Bax is found in the hepatocytes cytosol then moving to the mitochondria to promote apoptosis, hence the role of Bax is beat off by anti-apoptotic markers (Bcl-2 and Bcl-xL) as reported by Edlich et al. [90]. MO treatment caused up-regulation of Bax expression and down-regulation of Bcl-2 and Bcl-xL expression that promoted cancer cell apoptosis.

α-Fetoprotein (AFP) is a protein produced in developing fetus liver and then decreased gradually grown-ups [91]. DEN induces the expression of AFP [92]. Carcinoembryonic antigen (CEA) is an immunoglobulin supergene that is used al laboratory as a diagnostic tumor marker for the presence of numerous types of cancer [93]. The augmentation of CEA and AFP expressions as a result of DEN injection were connected with augmentation of cancer evolution. The inhibition in these markers due to MO treatment could be due to the recession of tumor generation rate via the achievement of antioxidant activity and induction of apoptosis [87].

Another investigation reported by Saalu et al. [94] showed that DEN caused inhibition GSH levels and decrease the activities of antioxidation enzymes due to the excessive lipid peroxidation (LPO) as a result of DEN metabolism. These effects were opposed by MO treatment; which causing the elevation of GSH and related antioxidant enzymes which a crucial mechanism of action of MO against DEN. The phenolic and flavonoid compounds found with large quantities in MO leaves (~2- and 3-fold) over other vegetables [95]. These compounds have powerful antioxidant activities; that causing free radicals scavenging, metal chelation, and enzymatic frameworks suppressing [49,96]. MO extracts were examined for their ability to induce NADPH:quinone oxidoreductase 1 (NQO1) activity on Hepa1c1c7 cells. NQO1 a detoxifying enzyme (phase II) that catalyzes the 2-electron inhibition of a wide range of chemicals especially quinones. The 2-electron reduction of quinones to hydroquinones by NQO1 is a detoxifying reaction since it bypasses the formation of the carcinogenic semiquinone and other chemicals, and protects cells against ROS generated by quinones [97]. Increased levels of NQO1 proportion with protection of carcinogenesis in the stage of promotion and initiation, so that NQO1 is used as phase II anti-carcinogenic marker to improve cancer chemo-preventive agents [98]. It was seen that MO could induce NQO1 levels due to the presence of antioxidant and polyphenol components. MO showed an anti-mutagenic activity versus 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide [45]. The main factor by which flavonoids and polyphenols induce NQO1 gene is controlled by the nuclear factor E2-related factor 2 (Nrf2). This induction of NQO1 occurred as a result of the presence of flavonoids [99,100]. Nrf2/ARE pathway activation occurred by non-flavonoids (sulforaphane and glucosinolate), or by polyphenols with antioxidant activity (kaempferol and quercetin) which has the prominent role of NQO1 gene augmentation [101]. This could be the mechanism for induced NQO1 cytotoxic activity and antiproliferation.

A potential oral anticancer drug of cold water extract of MO leaves induced apoptosis human hepatocellular carcinoma (HepG2) cells by activating caspase 3 via cleavage and down-regulating the expression of Bcl-xL anti-apoptotic protein [102]. Treatment of HepG2 cells with different concentrations of MO extract (0–200 µg/ml) showed an up to 70% inhibition in the number of colonies at a dose level of 50 µg/ml, reduction proliferation ratios in a concentration-dependent manner and reached up to 80% at a dose level of 200 µg/ml [103]. The expression of PARP and cleaved caspase-3 (apoptotic markers), were induced as a result of MO treatment. On the other hand, Bcl-xL (anti-apoptotic marker) expression was down-regulated, referring that MO extract have anti-proliferation activity in HepG2 cells due to DNA fragmentation and accumulation of cells at the G_0/G_1 peak. Jung et al. [102] showed that root bark extract from *M. concanensis* decreased HepG2 cell proliferation via fundamental pathways by up-regulating caspases 3 and 9 [104]. Activated compounds isolated from MO such as niazimicin and (4′-*O*-acetyl-α-*L*-rhamnopyranosyloxy) benzyl isothiocyanate proved their activities for the induction of caspase 9 activity [105].

NO is a free radical associated with fatty liver disease and is involved in hepatic lipid metabolism under starvation [106]. Therefore, the increase of NO production caused many deleterious to tissue function due to the ability of NO to react with free radicals *e.g.*, superoxide anion, giving the highly reactive peroxynitrite radical that have the ability to evoke the oxidation of important cellular biomolecules. The increased NO production caused also cellular toxicity that leading to the increase of lipid peroxidation. An ethanol extract of *M. stenopetala* seed and leaf induced HepG2 cytotoxiciy and induced LDH leakage in a time and dose-dependent manner [107]. When performed the HepG2 cells viability test and found that 2000-3000 mg/L of MO extract inhibited significantly the cancerous cell numbers. Therefore, the toxic effect of MO for cancerous cells could be due to the inhibition or stimulation roles through kinase signaling pathways, which affecting the cellular functions by changing the phosphorylation state of target molecules and by gene expression improving [108]. Other studies indicated that lower concentrations of flavonoids could lead to antioxidant response, including that of phase II detoxifying enzymes [109,110].

Phytochemical analysis of MO revealed the presence of isovitexin which has been reported to be responsible for inhibition of TNF-α level, MPO activity and MDA content as it occurs in animals with liver intoxication [111]. TNF-α is a multifunctional cytokine that in the liver acts as a mediator of the acute phase response and is a cytotoxic agent in many types of hepatic injury [112]. Moustafa et al. [113] evaluated the role of extract of MO leaves administration before the whole body-irradiated female rats with gamma-irradiation (LDR) on thioacetamide (TAA) to induce liver fibrosis. Gamma-irradiation of rats with 0.25Gy applied on the 1^{st} and 15^{th} day of the experiment. TAA treatment caused a significant increase in liver function enzymes, TNF-α, transforming growth factor (TGF-β) levels, MDA, NO, hydroxyproline, and gamma glutamyl transferase. These increase linked to the significant decrease of GSH content in liver. An improvement of liver damage was reported in rats treated with MO and/or LDR by reversing the result of the biochemical parameters and decreased fibroblast proliferation in the hepatic tissue.

3.3.3 Pancreatic cancer

Pancreatic cancer happens when uncontrolled cell growth begins in a part of the pancreas. Tumors develop, and these interfere with the way the pancreas works. Pancreatic cancer often shows no symptoms until the later stages, therefore it can be difficult to manage. According to the American Cancer Society [114], around 3% of all cancers in the United States are pancreatic cancers [115].

Hot water extraction of leaves of MO induced apoptosis in human Panc-1 pancreatic cell line by down-regulating expression of essential proteins of NF-kβ signaling pathway after 24 hours treatment. Also, p65, 1kβα and phosphor-1kβα were inhibited as compared with untreated control cells; leading to the increases the efficacy of chemotherapy in human pancreatic cancer cells [64]. MO extract from leaves cause an increase in the sub-G1 cell aggregation in PANC-1; this result proved the activity of MO to suppress growth of cancer cells due to its content of phytochemical compounds that target cancer cells only via cell cycle arrest [64].

Boreddy et al. [116] tested a compound named benzyl isothiocyanate (BITC) that isolated from *Moringa* flowers. This compound proved its activity to inhibit the proliferation of human pancreatic cancer cells by DNA damaging in G_2/M phase of cell cycle arrest and apoptosis; but not toxic to normal pancreatic epithelial cells [116] as conducted by Sahu and Srivastava [117]. This cytotoxicity feature delineated the participation of PI3K/AKT/FOXO pathway in BITC-induced cell death [118].

Mice were implanted BxPC-3 pancreatic cancer cell line and orally with 12 μmol BITC. BITC administration caused reduction in tumor growth by 43% via increasing apoptosis when compared with normal mice. The tumors from BITC-treated mice revealed inhibition in the phosphorylation of phosphoinositide 3-kinases (PI3K), phosphoinositide-3-kinase–protein kinase B/Akt (AKT), phosphatidylinositide 3-kinase (PDK1), and mammalian target of rapamycin (mTOR), forkhead box protein O1 (FOXO1), and forkhead box O3A **(**FOXO3A). Another study revealed that BITC treatment inhibited the expression of IKK-α in PanC-1and BxPC-3 cells, so that providing the evidence that BITC stimulate apoptosis by down-regulating AKT levels [116]. The concentration of BITC in plasma reached 6.5±0.1 μmol/L in the plasma after 1 hour of administration, and reached 7.5±0.3 μmol/g in the tumors in athymic nude mice after 46 days of BITC treatment. These levels proved the therapeutic activity of BITC [119].

3.3.4 Lung cancer

Lung cancer is a condition that causes cells to divide in the lungs uncontrollably. This causes the growth of tumors that reduce a person's ability to breathe. The presence of lung cancer is expected to increment due

to increase in exposure to airborne pollutants and cigarette smoke. Identifying lung cancer in its earliest stages can be difficult, because the symptoms may be similar to those of a respiratory infection [120].

A549 cells are cancerous alveolar epithelial cells. Al-Asmari et al. [76] reported that MO inhibited the growth of A549 cells at G2/M phase using 0.05% of leaves MO extracts after 24 h. These findings identify MO leaf extract as a potent anti-cancerous agent. ROS production and LDH release were also seen in A549 cells after MO treatment implying that MO extract exerts its cytotoxic effect through mitochondrial viability.

Treatment with extract from MO leaves revealed apoptosis in A549 lung cancer cells via mitochondrial and DNA fragmentation by activation of pro-caspase 3 to caspase 3 [12]. In a related observation, hot water extract of MO leaves induced apoptosis in A549 by up-regulating expression of pro-apoptotic proteins, p53, Smac/DIABLO, down-regulating anti-apoptotic protein (Nrf2) levels, and cleavage of PARP-1, increased activities of caspases 3,7 and 9 were observed in treated A549 cells [105]. MO reported a significant inhibition in mRNA and nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) protein expressions. The mRNA plays a fundamental role in synthesis of proteins [121], and Nrf2 is an antioxidant agent that preserves the cells from oxidative damage by regulating the synthesis of GSH [122,123]. The pro-apoptotic effect of MO was proved by the augmentation in p53 protein, p53 mRNA, caspase-3,7,9 and Smac/DIABLO activities [124,125]. Again; treatment with MO showed an activation and cleavage of PARP-1 into 24 KDa and 89 KDa fractions as reported by Tiloke et al. [105]. MO showed an anti-proliferative activity in A549 lung cells by inhibiting Nrf2 expression, increasing DNA fragmentation and apoptosis stimulation, and augmenting oxidative stress in cancer cells. The outcome is the increase in endogenous GSH antioxidant; and signals nucleases to cause DNA strand breaks which will result in ultimate apoptosis. The augmentation in oxidative stress is genotoxic to the cell. H_2O_2 react with ions like iron forming reactive hydroxyl radicals targeting DNA [126].

Thompson, [124] and Bertram [125] were investigated that increase in DNA damage and fragmentation related to the up-regulation of signals for apoptosis and repair. These signals for apoptosis take place via Bax (pro-apoptotic protein) activation, leading to mitochondrial depolarization, Smac/DIABLO releasing and cytochrome c releasing into the cytoplasm from the mitochondria. Apoptotic protease activating factor 1 (Apaf-1) and cytochrome c with ATP produce an apoptosome causing cleavage of pro-caspase-9 and induction of caspase-9, that consequently activates the caspases-3,7 that could contribute to the apoptotic pathway of MO.

Through apoptosis process, caspases are stimulated leading to the splitting of poly [ADP-ribose] polymerase 1 (PARP-1) [127]. PARP-1, a nuclear enzyme, is proteolysed to an 89 KDa C-terminal catalytic fragment and a 24 KDa N-terminal DNA-binding domain fragment [128]. The up-regulation of caspases 7 and 3 activities in A549 cells caused also cleavage of PARP-1 into 2 fragments [129]; which correlates with the induction of DNA damage by MO.

3.3.5 Breast cancer

Breast cancer is the most common among women and it is a deadly cancer worldwide [130]. Although, its survival rates are rising as screening and treatment improves, however, breast cancer is still the most invasive cancer in women.

Lacroix et al. [131] showed that eugenol from MO bark had a role in apoptosis in MDA-MB-231 breast cell line by up-regulation of Bax levels and down regulating the E2F Transcription Factor 1 (E2F1) protein revealed promising consequence in treating breast cancer [132]. A tangible induction in apoptotic cells numbers was reported when breast cancer cells treated with MO leaves and bark extracts. Berkovich et al. [64] delineated G2/M enrichment in breast cell lines treated with both bark and leaf extracts; these mechanisms of MO that responsible for cancer cell death could be attributed to the “shutting down” of various cancer survival pathways including the NF-Kβ signaling cascade by down-regulating the p65 of NF-kβ by the flavonoid and phenolic compounds present in *Moringa* extracts [64].

MO leaf, bark, and seed extracts possess a number of anti-cancer compounds that are responsible for their powerful anti-cancer effect versus MDA-MB-231 breast cell line, which delineated by a remarkable decrease in viable cells and decrease in cell number due to the presence of these chemical compounds. The cytotoxic effect is another mechanism of MO that contributes towards the change in the cellular phenotype [12]. The influences of seed, bark, and leaf MO extracts on cell motility were investigated in MDA-MB-231 and HCT-8 breast cancer cell lines. Cell motility inhibition is a mechanism of the anti-cancer effect of MO [76].

Leaf extract from *Moringa concanensis* reported a cytotoxic role versus MCF-7 (breast cancer cell line); by declined the cell growth and viability at a dose

level 200 µg/mL. This was joined by shape changes such as cell retraction, pyknotic nuclei, and blebbing [133]. The hexane fraction of crude ethanol extract from MO seeds [134] and proved its anti-proliferative activity (IC50 = 130 µg/mL) that were effective in its cytotoxic effect against MDA-MB-231and estrogen-positive breast cancer line MCF-7.

3.3.6 Ovarian cancer

Ovarian cancer is when abnormal cells in the ovary begin to multiply out of control and form a tumor. The tumor can spread to other parts of the body, if left untreated. This is called metastatic ovarian cancer [135].

MO roots have exhibited unique estrogenic, anti-estrogenic, progestational, and anti-progestational activities. Its effectiveness in treating ovarian cancer became apparent after the publication of many studies which demonstrating that benzyl (BITC) isothiocyanate and phenethyl isothiocyanate induce apoptosis in ovarian cancer cells *in vitro* [136].

Isothiocyanate of *Moringa* may inhibit proliferation of ovarian granulosa and other cells as it induces apoptosis via by a strong activation of caspase-3 and -9, and cleavage of PARP-1. It may also act by inhibiting ERK1/2 and Akt survival signaling while simultaneously activating pro-apoptotic p38 and JNK1/2. There are reports to show that *Moringa* induced decrease in cerebral dopamine and norepinephrine which may influence and lower nerve growth factor (NGF) and follicle-stimulating hormone receptor (FSHR) through central mechanisms. There is strong possibility of using this agent in epithelial ovarian cancer [137].

MO appears to be acting on some receptor, most likely the FSHR, because it initially increases estrogenic action when the uterus is enlarged. Then, it may inactivate this receptor locally or with the help of a central mechanism through NGF-mediated pathways [138]. Chronic treatment with MO significantly increased the 5-HT and decreased the dopamine and norepinephrine levels in the cerebral cortex, midbrain, caudate nucleus, and cerebellum [139]. As dopamine and norepinephrine influence NGF and FSHR through central mechanisms [138], this result may support their possible role in epithelial ovarian cancer. Vascular endothelial growth factor (VEGF) might also be involved via NGF [140].

BITC inhibited the proliferation of ovarian cancer cells and induced apoptosis. BITC showed a concentration dependent decrease in the levels of Bcl-2 with a concomitant increase in Bax levels. In addition, BITC activated pro-apoptotic signaling by phosphorylation JNK1/2 and p38 inhibiting survival signaling mediated by ERK1/2 and Akt phosphorylation at the same time that abolished the cytotoxic impact of BITC [141].

3.3.7 Prostate cancer

Prostate cancer considered as the most common type occurred in men. It is usually grows slowly, but sometimes it become aggressive and spread quickly that causing serious harm [142].

ITCs which known as a powerful anticancer agent, found in its precursor form, named glucosinolates, separated from MO extracts. Xiao et al. [143], reported that allyl isothiocyanates (AITC) treatement for 24 h inhibited the increase in human prostate cancer cell lines such as androgen independent (PC-3) and androgen dependent (LNCaP). The author found a relation between the presence of AITC and the inhibition of growth of PC-3 cells through the accumulation of cells at G2/M stage causing apoptosis. Another mechanism reported due to AITC treatment in fighting cancer was the down-regulation of CDK1 (a cyclin-dependent kinase-1 protein), CDC25B (a cell division protein), and CDC25C (which is M-phase inducer phosphatase 3 is an enzyme that in humans is encoded by the CDC25C gene. This gene is highly conserved during evolution and it plays a key role in the regulation of cell division). Boreddy et al. [116] showed that mice treated with BxPC-3 tumor xenografts with BITC and delineatd inhibition in tumor growth reached 43%, via the inhibition in phosphorylation of PI3K, pyruvate dehydrogenase kinase (PDK), AKT, FOXO3A, FOXO1, mTOR. Phenyethyl isothiocyanates (PEITC) showed a mechanism in reducing growth of cancer via the reduction of AKT [144]. MDA in the prostate gland was also significantly reduced 46.92% at the dose of 240 mg/kg of MO due to the presence of sitosterol and stigmasterol which lower a risk of prostate cancer [145]. Sulphoraphane, is one of the ITCs was reported to be responsible in increment of phase II enzymes expression at mRNA, protein and activity levels in cell lines. In human prostate cancer cells lines, when sulphoraphane was introduced, it helped to increase the cancer protective genes expression, NQO1 and glutathione S-transferase A1 (GSTA1), as well as the augmented activities of microsomal GSTA1 and NQO1 [146].

However, intrinsic and extrinsic pathways are interconnected with caspase-3 activation where activation of caspase-3 definitely leads to apoptosis [102]. It was reported that intervention of hormones

can contribute to extrinsic apoptosis, as example, testosterones hormone was reported to induce extrinsic apoptosis in prostate cancer when the hormone level is increased [147]. It is concluded that in balance concentration of the hormone, apoptosis will be inhibited and the hormone also can be an inducer of apoptosis. Intrinsic pathway is dependent on activation of p53, it is also a caspase independent pathway, because caspase also can occur by *in vivo* and *in vitro* cell ligands. Basically, in intrinsic pathway, when anti-cancer agent is introduced into the cell which it is permeable into mitochondria, Bcl-2 and Bax will be expressed. Bcl-2 and Bax are regulator protein in intrinsic pathway which release cytochrome c or apoptosis inducing factor (AIF) then apoptosis will occur. This pathway gave important beneficiary values. In the study of MO leaf extracts on human tumor cell line, the extract was able to cause a series of morphological changes such as membrane blebbing of the cells, cytoplasmic membrane shrinkage, loss of contact with neighboring cells, and apoptotic body formation which are the features to indicate apoptotic cell's death [63]. The morphological changes are caused by caspase substrate cleavage which is involved in apoptosis pathways.

3.3.8 Skin cancer

There are three major types of skin cancer which are basal cell carcinoma, squamous cell carcinoma and melanoma due to the exposure to ultraviolet (UV) radiation. Early detection of skin cancer gives the greatest chance for successful skin cancer treatment [148].

When skin response to Ultraviolet rays (UV) from sunlight abnormally; this condition is named as photodermatitis. Thurber and Fahey [149] suggested that when rats exposed to UV-B radiation caused epidermal thickening (hyperplasia) and thickening of the stratum corneum (hyperkeratosis) their skin. When irradiated rat treated with MO bark and leaf at a dose level of 400 mg/kg showed an inhibition in the epidermal thickness which proved the MO role in retarding the keratinocytes hyper-proliferation due to UV exposure. MO treatment produced beneficial changes in the epidermis of the irradiated skin. The pharmacological activities of MO may be due to its content of secondary plant metabolites such as sterols, glycosides, amino acids, alkaloids, flavonoids, phenolics, vitamins, carotenoids, and minerals. MO leaves contains phenolic acids such as quinic acid and chlorogenic acid that exhibit high antioxidant activities [38,150]. These compounds in the MO extract are responsible for the reduction of keratinocyte proliferation and enhancement of the keratinization process.

In addition, leaf extract administration of MO caused in a time-dependent increase of phosphor-extracellular signal-related kinase (p-ERK)and phosphor-c-Jun N-terminal kinase (p-JNK), but not affecting total JNK or ERK protein, that delineated MO pro-apoptotic role through the stimulation of these kinases A2058 cells (human melanoma cells) [85]. The anticancer activity of MO against B16 F10 melanoma tumors in mice were conducted by Purwal et al. [151], the authors delineated that 500 mg/kg/bw delayed growth of tumor. This activity was related to the presence of phytochemicals such as niaziminin, quercetin, and niazimicin. Treatment with leaf extract from *M. oleifera* reported to decrease B16F10 melanoma cell proliferation and induce cancerous cell death (22%) as reported by Gismondi, et al. [152]. The apoptosis occurred at the sub G1-area and motivated cell stop at the G2/M phase, augmented the p21WAF1/Cip1, p27Kip1, and p53 levels of the cells.

Bharali et al. [153] evaluated the curing effect of the MO extract against UV-B exposure that utilized to induce psoriasis in rats. The authors found a considerable difference in skin epidermal thickness. Different doses 200 and 400 mg/kg from MO extracts caused an increase in the rate of re-epithelisation and wound healing of skin cells. MO also promoted fibroplasia, decreased inflammation and formed high amounts of scar tissue. These mechanisms of MO extract were successful in fighting psoriasis changes in rats as compared with the irradiated rats [148].

4. CONCLUSION

In conclusion, *Moringa* is an anti-cancer and an immune-boosting agent that inhibit cancer cell proliferation leading to kill these cells. The main mechanism of *Moringa* against fighting cancer is by down-regulation cancer cell proliferation through apoptosis. The results of this review suggest that *Moringa* may be associated with its contents of various types of phytochemical compounds, which have also many beneficial effects as a chemo-preventive agent. The mechanisms of action summarized in Fig. 10.

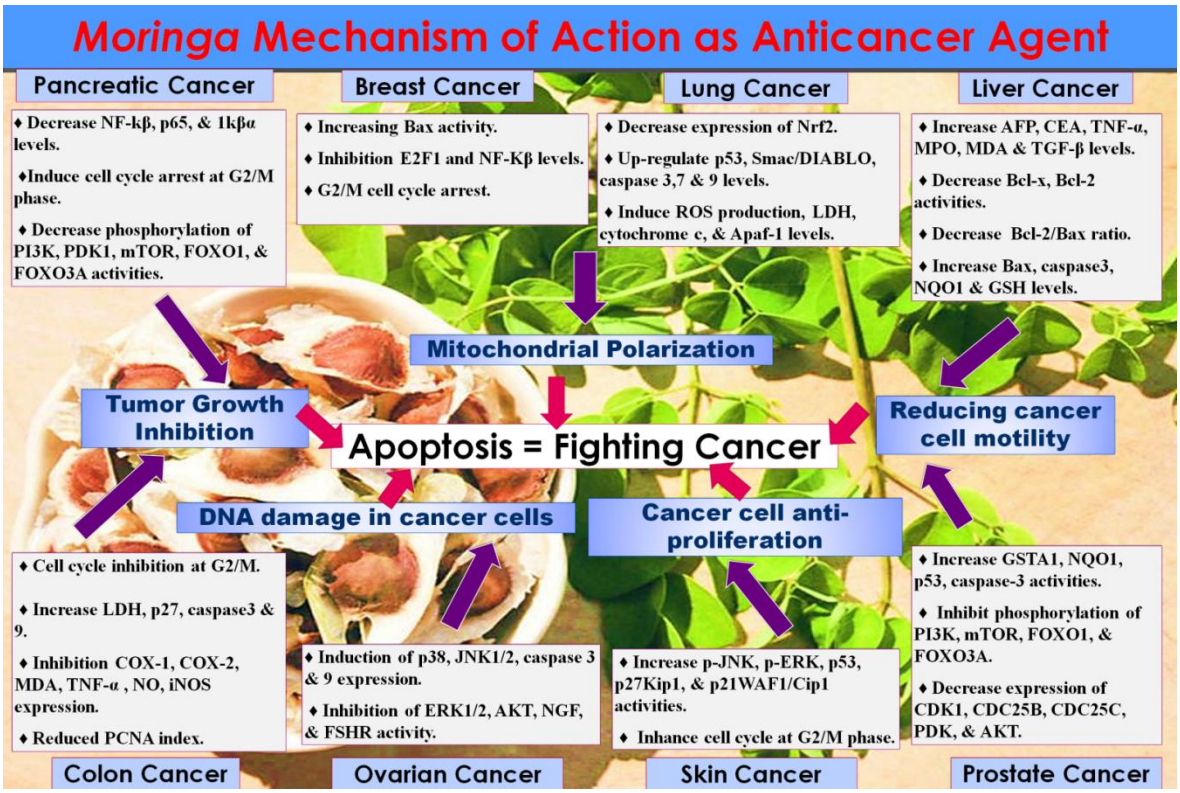


Fig. 10. Diagram summarizes the mechanism of action of *Moringa* as fighting agent against different types of cancer (Original picture)

COMPETING INTERESTS

Author has declared that no competing interests exist.

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