Indian Journal of Biochemistry & Biophysics
Vol. 57, April 2020, pp. 127-145

A Review

Trianthema portulacastrum L.: Traditional medicine in healthcare and biology

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Received 25 October 2019; *revised 26 January 2020*

Medicinal plants are the major folk and traditional medicine for the prevention of diseases worldwide. *Trianthema portulacastrum* L. (family: Aizoaceae), a small perennial weed, found in the America, Africa, India, and other regions of the world, and are extensively used not only as medicine but also as vegetable for its various health benefits. Phytochemical analysis of *T. portulacastrum* reveals the presence of alkaloids, phytosterols, terpenoids, saponins, flavonoids and phenolic compounds. *In vitro* and *in vivo* studies have demonstrated its pharmacological and biological activities. Different parts of *T. portulacastrum* L. are conventionally being used as analgesic, anti-pyretic, lipid lowering and microbicide agent; and protect liver and kidney from carcinogen, inflammation and oxidant chemicals.

Keywords: Antioxidant, Anti-inflammation, Hepatoprotective, Phytochemicals, *Trianthema portulacastrum* L.

Introduction

Medicinal plants are the major folk and traditional medicine for the prevention of diseases worldwide, especially in underdeveloped and developing countries, where the modern scientific treatment and therapies are challenging or expensive[1-3]. The global demand for herbal medicine is increasing. Compounds isolated from different herbs are used as key components to treat various diseases. A major share of FDA approved drugs has been reported directly or indirectly is based on natural products[1]. Many synthetic molecules resemble structural homology with various natural products that serve as leads[4]. India is the rich source of traditional medicinal systems, where out of 2500 species of medicinal plants, 150 species are harvested for commercial use on a grand scale[5,6].

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Abbreviations: ACE, Angiotensin Converting Enzyme; AFB1, Aflatoxin B1; CA, caffeic acid; CAPE, Caffeic acid phenethyl ester; CCl_4, Carbon tetrachloride; DENA, Diethylnitrosamine; DMBA, 7,12-dimethylbenz[a]anthracene; DPPH, 1,1-diphenyl-2-picryl hydrazyl; FA, Ferulic acid; FLT3, Fms-like Tyrosine Kinase 3; GLUT, Glucose Transporter; HCC, Hepatocellular Carcinoma; HO-1, heme oxygenase-1; MDR, Multidrug resistance; NAFLD, Non-alcoholic fatty liver disease; NAPQI, N-acetyl-p-benzoquinone; NF-κB, Nuclear factor-kappa B; Nrf2, Nuclear factor (erythroid-derived 2)-like 2; PDGFR, Platelet-Derived Growth Factor Receptor; PHBA, p-hydroxy benzoic acid; ROS, Reactive oxygen species; RTK, Receptor Tyrosine Kinase family; STZ, Streptozotocin; TA, Thioacetamide; TASO, Thioacetamide S-oxide; $TASO_2$, Thioacetamide S,S-dioxide; TNF-α, tumor necrosis factor-α; VA, Vanillic acid

Trianthema porulacastrum L.

Trianthema porulacastrum L. is a well-known medicinal plant used from ancient time to treat several diseases. *T. portulacastrum* L. (also called *Trianthema monogyna* L.)[7], (family of Aizoaceae, also known as horse purslane, Bishkhapra, carpetweed, Punarnava, Gadabani and Labuni) has historically been valued by Indian and African cultures for its numerous medicinal properties[8,9]. The herb is found worldwide *e.g.* Southeast Asia (India, Bangladesh, Sri Lanka, Pakistan, *etc*.), Africa (like Ghana and Tanzania) and America. It grows in sunny desert as well as in irrigated and tropical rainfall areas. It's over growing nature is common in agricultural field especially in rainy seasons[10,11].

Botany

T. portulacastrum is considered as annual or perennial depending on geographical area and the plant is propagated by seeds but the fragments of the stem can be spread by cuttings very easily. The plant is often succulent, branched, annual terrestrial and prostrate herb that produces colored flower (red or white color). Two varieties of the plant are found, one is red-flowered variety known as 'Rakta Punarnava'

or 'Lal Sabuni' and white-flowered one is known as 'Shwet Punarnava' or 'Svet Sabuni'; and the former is more abundant[8]. The flowers are small, solitary, bisexual, pale pink or white in color and have stamens and white filaments. Both types are grown best under partial shade and flourish in neutral to alkaline soil. Few vernacular names are listed in (Table 1)[12-14].

The roots are thin, tortuous, slender, lateral branching fibrous. The leaves are succulent, green, opposite, oval shaped and unequal in size. The stems are branched, cylindrical, fleshy and angular to some extent and prostrate in nature. Fruit is circumsessile capsule like shaped that partly exerted from partial perianth containing 2-8 seeds. The seeds are hairless, kidney-shaped 1.5-2.5 mm long and black in color[7,12,15]. Pictorial form of the plant is shown in (Fig. 1).

Nutritional value

Trianthema portulacastrum L. is commonly used as vegetable in East Asian countries including India and in African countries especially, in Ghana, Cameroon and Tanzania[9]. This edible wild plant is a good source of carbohydrates, protein and minerals[16-18]. *Trianthema portulacastrum* L. contain approximately 9% crude protein[18], 3% carbohydrate[16], and supply nearly 76 kcal energy/ 100 g[16]. This plant is easily digestable due to its simple structural carbohydrate in cell wall[19]. Storage form of energy (lipid) is about 2%[16]. The leaves of *T. portulacastrum* contain nearly 43% of crude fiber[20].

Table 1 — Vernacular names:[Anonymous 2003; Shanmugam 2007; Zihad *et al*. 2019] [12-14]

Language	Name of *Trianthema portulacastrum* L.
English	Horse Purslane
Bengali	Gadabani, Swet punarnova, Kulpasag
Hindi	Santhi, Sabuni, Vishakhapara, Lalsabuni, Svetsabuni
Sanskrit	Shvetapunarnava, Chiratika, Dhanapatra, Shvetamula, Upothaki
Tamil	Sharunnai, Shavalai
Telegu	Ambatimadhu, Atikamamidi, Galijeru
Bombay	Svetapunarnava
Punjab	Bishkapra, itsit
Kan.	Muchchugoni
Mal.	Sharunnau
Madras	Mukkarattai
Marathi	Pundharighetntuli
Urdu	Narma

Vitamin A (~0.8 mg/g), vitamin B_2 (~2.02 mg/g)[16], Vitamin B_3, vitamin C[21], sodium (~44 mg /g), potassium (~51.6 mg/ g), copper (~20 mg/kg), zinc (~200 mg/kg), nickel (~30 mg/kg), iron (~6.44 mg/g) and manganese (40 mg/kg) were found in *T. portulacastrum*[16].

Different parts of *T. portulacastrum* are used traditionally as valuable source for pharmacological components that is used to treat alcohol poisoning, liver ailments, bronchitis, heart diseases, asthma, ascites, anemia, beri-beri, dropsy, corneal ulcers, edema, inflammation, migraine, rheumatism, piles and night blindness[17,21,22]. Both adverse and beneficial effects of *T. portulacastrum* ingestion have also been reported particularly in consumption of old leaves. It is reported that the consumption of old leaves causes diarrhea and paralysis both in humans and also in domestic animals. Seeds are also reported to have harmful effects[9]. But old leaves of *T. portulacastrum* are used to treat gonorrhea in Nigeria[23]. On the contrary, the root is used for diseases of the liver, spleen, and malignancy, while its leaves have been used for the treatment for diuretics diseases like edema and ascites in India, Africa and Asia[7]. The root is applied for the treatment of eye disorders like itching, corneal ulcer, night blindness and dimness of sight[22].

Phytochemicals

Trianthema portulacastrum L. contains a wide range of secondary metabolites like carbohydrates, fats, tannins, terpenoides, flavonoides, steroids, alkaloids, saponins, cinnnamic acid derivatives and benzoic acid derivatives[24-27]. The main constituent tetraprenoid (trianthenol; 15-hydroxymethyl-2, 6, 10, 18, 22, 26, 30-heptamethyl-14-methylene-17-hentriacontene) was isolated from chloroform extract having anti-fungal property[24]. Four more compounds such as 3-acetyl aleuritolic acid, 5-hydroxy-2-methoxy benzaldehyde, p-propoxy benzoic acid and p-methoxy benzoic acid were also reported[24]. Other tetraterpene and β-carotene were also reported[21].

Hydrocarbons were isolated from fresh leaves surface wax using gas liquid chromatography[28]. Total phenolic content varied within 50-98 mg gallic acid equivalents/g of dry weight. The flavonoids include 5,2′-dihydroxy-7-methoxy- 6,8-dimethylflavone (*C*-methylflavone) and 5,7- dihydroxy-6,8-dimethyl chromone (leptorumol)[27]. Few plant sterols, such as stigmasterol, β-sitosterol and β-glucopyranosides were isolated from dried plant[27]. Alkaloids like trianthemine and punarnavine also found in this plant[29].

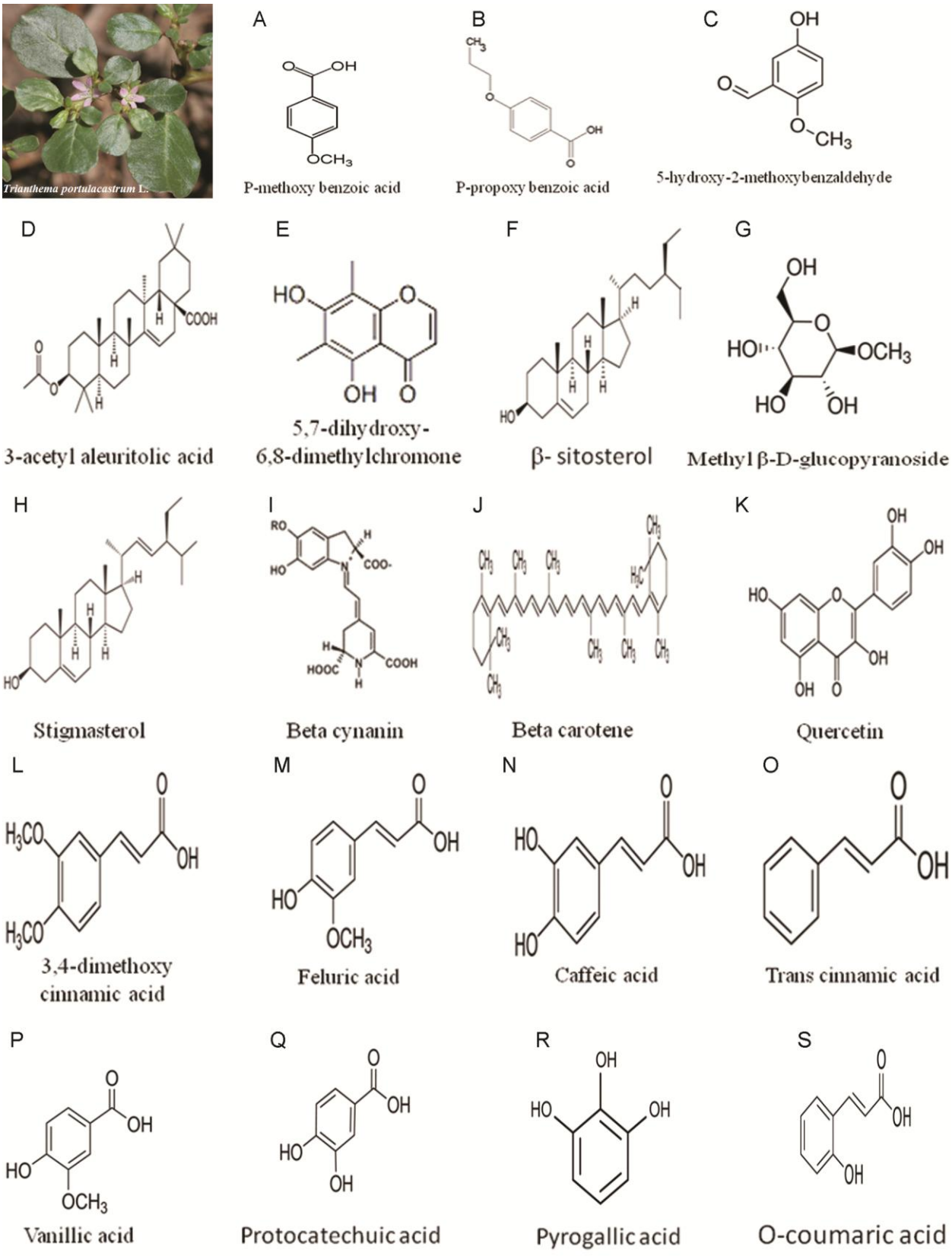

Fig. 1 — Phytochemicals available from *Trianthema portulacastrum* L.

Ecdysterone a plant steroid has been isolated from the whole plant[30]. The red pigment β-Cyanin and 3,4-dimethoxy cinnamic acid have been reported from this plant[31]. Others phytochemicals isolated from different parts of *T. portulacastrum* include vanillic acid, ferulic acid, p-hydroxybenzoic acid, protocatechuic acid, caffeic acid, pyrogallic acid and o-coumaric acid[32].

Biological activities of different phytochemicals available from *T. portulacastrum*:

a. **p-Methoxybenzoic acid** exhibited hepatoprotective activity against carbon tetrachloride (CCl_4) and paracetamol induced hepatotoxicity *in vivo*, and thioacetamide and galactosamine-induced hepatotoxicity in isolated rat hepatocytes[33, 34].
b. **p-hydroxy benzoic acid (PHBA)** has antimicrobial, antialgal, antimutagenic, antiestrogenic, anti-inflammatory, anti-platelet aggregate, nematicidal, antiviral, antioxidant and hypoglycemic activities. It finds use in cosmetic products, pharmaceuticals, drugs preservative and food and beverages industry[35-37]. Derivatives of PHBA inhibit oedema induced by acetic acid and is used in sickle cell disease[35].
c. **5-hydroxy-2-methoxybenzaldehyde** acts as an essential compound for the formation of bis (benzo[b]furan-2-yl)methanones that inhibit FLT3 (Fms-like tyrosine kinase 3) and PDGFR (platelet-derived growth factor receptor) which have been implicated in numerous pathological conditions like cancer and are the members of receptor tyrosine kinase (RTK) family[38].
d. **3-acetyl aleuritolic acid:** Acetyl aleuritolic acids showed effect against *S. aureus* and *S. typhimurium*[39]. It also showed tumor-inhibitory properties toward the P-388 lymphocytic leukemia test system[40]. 3-O-acetylaleuritolic acid inhibited the proliferation and migration of cancer cell lines as well as contributed to autophagy induction showing some anticancer properties[41], and exhibited significant inhibitory activities on the vitality of adult male worms of *O. gutturosa*[42].
e. Anti-proliferative activity of 5,7-**dihydroxy-6,8-dimethyl flavanone** was evaluated on human colon cancer (HCT 116) cell line[43].
f. **Phytosterols (β-Sitosterol, Stigmasterol)** are widely present in vegetable oils, nuts, cereal products, fruits, and berries. Phytosterol compounds reduce the inflammatory reaction in LPS-induced macrophage models; and also inhibit the expression and activity of pro-inflammatory mediators[44].

β-sitosterol, the most common dietary phytosterol, lowers the cholesterol levels, enhances the production of plasminogen activators, and exhibits anticancer and antiatherogenic effects[45]. It enhances glycemic control by increasing the activation of insulin receptor and glucose transporter 4 (GLUT4) proteins in adipose tissue. In Silico analysis showed that β-sitosterol possesses the greater binding affinity with β-arrestin-2, c-Src, and IRS-1 as well as Akt proteins and attenuate insulin resistance. It also attenuates high fat diet-induced detrimental changes in adipose tissue[46]. It has been associated with cardiovascular protection by increasing the antioxidant defense system and effectively lowering the serum cholesterol level. It inhibits vascular adhesion molecule 1 and intracellular adhesion molecule 1 expression in TNF-α-stimulated human aortic endothelial cells[47].

β-sitosterol shows anti-inflammatory activity[48]. It can modulate the functions of macrophages and might be a promising agent for rheumatoid arthritis therapy[49]. It mediates the p53/NF-κB/ breast cancer resistance protein signaling axis and regulates the response of colorectal cancer to chemotherapy[50]. β-Sitosterol can prospectively be used to mitigate diet-induced non-alcoholic fatty liver disease (NAFLD)[51]. It is useful for prevention of Alzheimer's disease, ameliorates memory and learning impairment in APP/PS1 mice and possibly decreases Aβ deposition[52]. It also contributes to the development of the compounds as anti-aging ingredients[53].

Stigmasterol showed antioxidant[54], anti-inflammatory, hypoglycemic effect[48] and antimicrobial activity[55]. It promoted transintestinal cholesterol secretion[56]. It has neuro-protective effect against the ischemic/reperfusion (I/R) injury, possibly associated with reduction of oxidative stress and inactivation of autophagy *via* AMPK/mTOR and JNK pathways[57]. It also inhibited growth of gastric cancer cells[58]. It acts as a precursor in the synthesis of progesterone and acts as an intermediate in the biosynthesis of androgens, estrogens, corticoids and in the synthesis of vitamin D_3[59,60].

g. **β-D-glucopyranoside** derivative has been reported against influenza virus (H1N1)[61].

h. Nitrogen-containing **β-cyanins** (red-violet) has been used as colorant in cosmetics and pharmaceuticals[62]. It is a scavenger of reactive oxygen species and exhibits gene-regulatory activity partly *via* nuclear factor (erythroid-derived 2)-like 2-(Nrf2) dependent signaling pathways. This may induce phase II enzymes and antioxidant defense mechanisms[62].

i. **β-carotene**, important precursors of retinol (vitamin A), quench highly reactive singlet oxygen under certain conditions and can block free radical-mediated reactions[63,64].

j. **Quercetin** and its main derivatives, such as rhamnetin, rutin, hyperoside, *etc*., are the major polyphenolic flavonoid found in food products, including berries, apples, cauliflower, tea, cabbage, nuts, and onions that have traditionally been treated as anticancer and antiviral, and used for the treatment of allergic, metabolic, and inflammatory disorders, eye and cardiovascular diseases, and arthritis. It has been examined against several pathogenic bacteria, viruses and parasites. It has shown beneficial effects against Alzheimer's disease, due to its inhibitory effect against acetylcholinesterase[65]. It is known for its free radical scavenging activity, anti-inflammatory, anti-hypertensive, vasodilator, anti-obesity, anti-hypercholesterolemic and anti-atherosclerotic activities[66,67]. These critical properties of quercetin are responsible for anti-diabetic effect[68] and controlling the pathogenesis of NAFLD[69]. In addition, its effect on proliferation, angiogenesis, or apoptosis, are considered as anti-tumor property to enhance breast cancer treatment[70]. Quercetin also demonstrated a significant protective effect on metronidazole-induced neuronal toxicity[71].

k. **3,4-dimethoxy cinnamic** acid has been reported to have anti-oxidant activity[34].

l. Plant derived **Ferulic acid (FA)** is an antioxidant phenolic compound. Ferulic acid phenoxyl radical is considered as stable and unreactive, which contribute it's overall antioxidant activity[72]. It prevented methotrexate-induced hepatotoxicity by activating Nrf2/HO-1 (heme oxygenase-1) signaling and PPARγ, and attenuating oxidative stress, inflammation and cell death[73]. FA and derivatives acted as platelet aggregation inhibitor, tyrosinase-inhibitor, angiotensin converting enzyme (ACE) inhibitor, and superoxide dismutase like activities, and are involved in repair of blood vessel injury like thrombosis[74].

Ferulic acid causes cell cytotoxicity and apoptosis of HeLa and Caski cells, and the PI3K/Akt signaling pathway is down-regulated in Caski cells[75]. It preserves self-renewal in embryo stem cells, and contributes to adipose-derived mesenchymal stem cells self-renewal and effective weight control in obesity[76]. FA suppressed benzo(a)pyrene -induced toxicity in microglia, and exert neuroprotective effects by inhibiting microglia-mediated pro-inflammatory response[77].

Symptoms of osteoporosis include a reduction in bone strength, osteopenia, and damage to the bone microstructure. FA suppresses the fusion and apoptosis of mature osteoclasts, increase the mRNA and protein levels of SIRT1, reduced expression of nuclear factor-kappa B (NF-κB), and increase bone mineral density[78].

m. **Caffeic acid** (3,4-dihydroxycinnamic acid) showed antioxidant, anti-ischemia reperfusion, anti-thrombosis, antihypertension, anti-fibrosis, antivirus and antitumor properties[79]. Caffeic acid (CA)-treated mice exhibited significantly lower levels of 4-hydroxynonenal, an oxidative stress marker in the hippocampus, but no effect on the expression levels of neurotrophic factors and inflammatory or anti-inflammatory cytokines, as well as significantly fewer activated microglia[80]. It can be used to treat folliculitis, usually caused by a bacterial or fungal infection, due to its antioxidant potential and antimicrobial properties[81]. CA can prevent and delay the advanced glycation end products-induced vascular dysfunction in diabetes[82]. It can down regulate the miR-636 expression level, which is involved in development of diabetic nephropathy[83]. CA stimulates the expression of detoxification enzymes such as regulates HO-1, and glutamate-cysteine ligase through the ERK/Nrf2 pathway, and it may be an effective chemoprotective agent for protecting liver damage against oxidative damage[84]. Caffeic acid has induced toxic effects and morphological changes in breast cancer cells *via* apoptosis[85].

Multidrug resistance (MDR) is a complicated ever-changing problem in cancer treatment, and P-glycoprotein (P-gp), a drug efflux pump, is regarded as the major cause. Caffeic acid is a promising candidate for P-gp inhibition and cancer MDR attenuation[86]. It can alleviate the cell damage

induced by overexpressing A53T α-synuclein and that CA reduced A53T α-synuclein by activating the JNK/Bcl-2-mediated autophagy pathway[87].

Caffeic acid phenethyl ester (CAPE) has various biological activities including antioxidant and anti-inflammatory effect. CAPE decreases the bone resorption, enhances the bone healing, prevent alveolar bone loss and stimulate periodontal tissue healing[88]. CAPE significantly induces mRNA expression and production of VEGF in rat clonal odontoblast-like KN-3 cells cultured in normal medium or osteogenic induction medium. CAPE treatment enhances NF-κB transcription factor activation; up regulates the expression of VEGF receptor-2 and increase mineralization activity in KN-3 cells, and might be useful for the dental pulp conservative therapy[89].

Androgen receptor (AR) plays important role in the development, progression, and metastasis of prostate cancer and CAPE treatment reduces AR stability and AR transcriptional activity in PCa cells[90]. Caffeic acid esters are potent bactericidal compounds against *Paenibacillus* larvae and eliminate bacterial growth through an oxidative stress mechanism[91]. It is also a promising agent for the prevention of skin photoaging[92].

n. **Cinnamic acid** and derivatives have multipurpose functions, such as drugs for anti-tuberclosis, antidiabetic, antioxidant, antimicrobial, hepato-protective, CNS depressant, anti-cholesterolemic, antifungal, fungitoxic, anti-hyperglycemic, antimalerial, antiviral, anxiolytic, cytotoxic, anti-inflammatory and UV rays absorbent[93]. Trans-cinnamic acid showed effect against colon cancer in xenograft nude mice. Trans-cinnamic acid inhibit histone deacetylases in cancer cells[94].

o. **Vanillic acid** (VA), an oxidized form of vanilla, is a flavoring agent. VA improves oxidative stress in endothelial cells stimulated by palmitic acid by activating AMPK and its downstream proteins, and protect from diabetic vascular complications[95]. VA exerts cardioprotective effects against Doxorubicin-induced cardiotoxicity by decreasing oxidative stress, suppressing TLR4 signaling and consequently inflammation pathway[96]. Anti-inflammatory and antioxidative properties of vanillic acid are associated with neuroprotective effects, resulting from Akt or ERK signaling activation. The activation of the mammalian target of rapamycin (mTOR), a key downstream target of Akt and ERK signaling, is a crucial therapeutic target for treating depression[97]. It alleviates osteoarthritis progression in a rat model by suppressing the IL-1β induced activation of MAPK and PI3K/AKT/NF-κB pathways[98].

Vanillic acid has a potent antibacterial and antibiofilm activity against carbapenem-resistant Enterobacter hormaechei and potential to be used in the food industry as a food preservative and surface disinfectant[99]. VA and derivatives have antihelmintic and antisickling activities, and suppress hepatic fibrosis in chronic liver injury[100,101].

p. **Protocatechuic acid (PCA)**, a complex polyphenols of anthocyanins and procyanidins, possesses antioxidant, anti-inflammatory as well as antihyperglycemic and neuroprotective activities[102], antibacterial, anticancer, anti-ageing, anti-atherogenic, anti-tumoral, anti-asthma, antiulcer, antispasmodic and neurological properties[103]. PCA also have chemopreventive activity as it can inhibit anti-proliferative and pro-apoptotic effects induced by chemical carcinogenes[102].

Protocatechuic acid and its alkyl esters ethyl protocatechuate are promising candidates for the prevention and treatment of UVB-induced skin photodamage and photoaging caused by generation of reactive oxygen species (ROS)[104]. PCA-stimulated miR-219a-5p expression mitigates alcoholic liver disease by reducing p66shc-mediated ROS formation[105].

SIRT1 exhibits inhibitory effects on microglial activation-induced neurodegeneration. PCA inhibited the release of inflammatory mediators in LPS-activated BV2 microglia *via* the SIRT1/NF-κB pathway and thereby attenuated microglial activation-induced PC12 cell apoptosis[106]. It has potential to prevent Alzheimer's disease[107].

Protocatechuic acid attenuated anterior cruciate ligament transection-induced osteoarthritis by suppressing osteoclastogenesis by inhibiting the MAPK, ATK and NF-κB signaling pathways[108]. It shows protection against anticancer drug methotrexate-induced hepatorenal toxicity *via* antioxidant, anti-inflammatory, and antiapoptotic mechanisms[109]. Another study suggested that phytochemicals having antioxidant efficacy is responsible for detoxification[110].

q. **Pyrogallic acid** has anti-bacterial (cyanobacteria) activity[111,112] and can also regulate the bacterial gene expression[112]. It is used in various industrial and consumer products. PA is autoxidized to

purpurogallin (PG), which is further autoxidized to other polyphenolic compounds. PA and PG might participate a futile redox cycle, which mediated ROS-induced toxicity in *M. aeruginosa* through oxidative damage to DNA strands and cell membrane[113].

r. **O-coumaric acid** has limited biological activity. It exerts anticarcinogenic and chemopreventive activity in human breast cancer cell (MCF-7) line. It showed regulatory role on p53 protein, Caspase-3 protein and Bax and Bcl-2 protein and mRNA levels[114].

Toxicity study

No toxicity was observed at dose of 3g/kg in mice model[25, 31]. No mortality was observed at dose of 4 g/kg with methanolic extract of whole plant in rat model[115]. No atypical behavior was observed after intraperitonial administration of ethanolic extract at a dose of 250 mg/ kg in Swiss albino mice[13].

Pharmacological Activities

Hypolipidemic activity

Dyslipidemia is associated with cardiovascular diseases, obesity and other metabolic disorders[116]. *T. portulacastrum* exhibited the hypolipidemic activity by controlling triglyceride, total cholesterol, LDL-cholesterol and HDL-cholesterol in blood[117] (Table 2).

Antimicrobial properties

Plant extracts are reported to exhibit antibacterial activities[118]. *T. portulacastrum* showed anti-bacterial and anti-fungal activity[119]. Ethanolic extract of *T. portulacastrum w*hole plant acted against gram positive bacteria[120]. Aqueous, methanolic and chloroform extracts showed antibacterial properties against *Escherichia coli*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Shigella flexneri*[26]. Root extract of *T. portulacastrum* exhibited antibacterial activity against *Proteus vulgaris*, *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*[121].

Trianthenol-1 isolated from chloroform extract of *T. portulacastrum* acted moderately against fungal pathogens[24]. The flavonoid fraction of chloroform and methanolic extracts of *T. portulacastrum* showed anti-fungal activity against human pathogens such as *Candida albicans*, *Aspergillus fumigates*, *A. niger*, *A. flavus* and *Rhizopus oryzae*, but showed no effect against *Mucor* spp[26].

Anthelmintic, larvicidal, hormonal and chemosterilant activity

Antihelmintic activity against *Haemonchus contortus* (female) and their eggs were observed by aqueous methanolic crude extract of *T. portulacastrum in vitro* and in sheep model after infecting with nematodes (roundworms) species *in vivo*[122]. Aqueous and acetone extract also showed larvacidal activity against *Culex quinquefasciatus*, *Anopheles stephensi* and *Aedes aegypti*[123].

Hormonal regulation of *T. portulacastrum* was reported in *in vivo* insect model[124,125]. Ecdysterone (phytoecdysone) from *T. portulacastrum* (whole plant) demonstrated chemosterilant activity through molting hormonal activity in larvae of house fly (*Musca domestica*)[124].

Antifertility activity

Chloroform, aqueous and alcoholic extract of *T. portulacastrum* leaves, stem and roots acts as a potential pregnancy interceptive, at dose of 100, 200 and 400 mg/kg body weight[23].

Analgesic, antipyretic and antinociceptive activity

Ethanolic extract of *T. portulacastrum* whole plant elicited considerable reduction on writhing response in acetic acid induced mice. 250 mg/kg of such extract demonstrated similar effect like aspirin[13]. Podo dolorimeter measurement (measure voltage threshold) showed significant result in mice; however thermal caudal immersion and mechanical tail clip techniques failed to reveal any fruitful result[120]. The extract also had antinocicepative activity equivalent to drug aspirin in mice determined by hot-plate reaction time model[13]. Antipyretic activity of *T. portulacastrum* was observed by whole plant ethanolic extract (50 mg/kg, *i.p.*) in rat induced by yeast pyrexia[120].

Nephroprotective, Diuretic and Antilithiatic activity

Ethanolic leaf extract of *T. portulacastrum* showed protection against nephrotic syndrome induced by adriamycin[126] (generic name doxorubicine, a drug used to treat cancer patients) and gentamicin[127] (drug known as aminoglycoside, used to treat wide range of bacterial infection) in rat by decreasing blood urine nitrogen, serum chloresterol and creatinin level, and by increasing serum protein and albumin level. Methanolic extract of *T. Portulacastrum* showed nephroprotective

Table 2 — Pharmaceutical Activity

Plant extract type	Animal model & Microorganism	Dose (body weight)	Study time	Route	Toxic control	Result	Reference
Ethanolic	Female Sprage Dawley Rat	50,100, and 200 mg/kg	16 week	p.o.	7,12-dimethylbenz (a) anthracene	Chemopreventive activity against brest cancer	204
Ethanolic	Male wistar rat	100 mg/kg	7 day	p.o.	Aflatoxin	Hepatoprotective	181
Ethanolic	Male wistar rat	100, 200 mg/kg	21 day	p.o.	Aflatoxin	Antihepatotoxic	180
Ethanolic	Male and female wistar rat	100, 200 mg/kg	10 days	p.o.	Thioacetamide and paracetamol	Hepatoprotective	161
Ethanolic	Male Swiss albino mice	150 mg/kg	13 week	p.o.	CCl4	Hepatoprotective	171
Ethanolic	Male Swiss albino mice	50, 100, 150 mg/kg	3 days	p.o.	CCl4	Hepatoprotective	169
Ethanolic	Male Swiss albino mice	100, 150 mg/kg	7 week	p.o.	CCl4	Antihepatotoxic effect	150, 151
Ethanolic	Male and female wistar rat	100, 200 mg/kg	2 week	p.o.	Thioacetamide (150 mg/kg) and paracetamol (3 g/kg)	Antioxidant	162
Ethanolic	Male wistar rat	100, 200 mg/kg	10 days	p.o.	Atherosclerotic diet	Renoprotective and Hepatoprotective	128
Ethanolic	Mice	-	7 days	-	Aspirin and Acetic	Analgesic activity and antin ociceptive activity	13
Metanolic	*In vitro*	10 µL		-		Free radical Scavenging	134
Methanolic	*In vitro*	1,10,100,1000, 2000,5000 µg/mL				Radical scavenging and anti-oxidant activity	135
Methanolic	Wistar albino rats	100, 200, 300 mg/kg	7 days	*i.p.*	Alloxen	Hypoglycemic and hypolipidemic	117
Methanolic	Male wistar albino rat	100, 200 mg/kg	7 days	*p.o.*	Streptozocin	Antihyperglycemic	31
Aqueous methanolic	Male & female sheep	1,4 & 8 g	15 days	*p.o.*	-	Anthelmintic	122
Aqueous	Albino rat	10, 30& 50 mg/kg	-	*i.p.*	-	Antidiuretic	25
Aqueous, alcoholic &chloroform	Female wistar rat	100,200 & 400 mg/kg	5 day	*p.o.*	-	Antifertility activity	23
Aqueous, ethanolic and chloroform	Male Sprage Dawley Rat	100, 200 mg/kg	22 week	*p.o.*	Diethynitroso-amine	Anticarcinogenic	127, 207, 208
Aqueous and ethanolic	*In vitro* (paper disc diffusion)	20 µL				Antibacterial activities	209
Chloroform	*In vitro* (Candida Albicans, *A. fumigatus*	20 µL	2 days	-		Antifungal	24
Aqueous & acetone	Culex Quinquefasciatus, Anopheles stephensi and Aedes aegypti	1, 0.75, 0.75 and 1%	4 week	-	-	Larvacidal	123
Whole plant	*In vitro*	-	-	-	-	Fodder potential & nutritive value	19

(*Contd.*)

Table 2 — Pharmaceutical Activity

Plant extract type	Animal model & Microorganism	Dose (body weight)	Study time	Route	Toxic control	Result	Reference
Aqueous, methanolic and chloroform	*In vitro* (bacterial and fungal)	20 µL	48 h	-		Antifungal & antibacterial activity	26
n-butanol, hexane, chloroform and ethyl acetate	*In vitro* (bacterial and fungal)	20 µL				Antifungal & antibacterial activity	119

effect in renal injury, damged by artherosclerotic diet in rat[128].

Aqueous extract of *T. portulacastrum* showed significant diuretic activity against non-treated and furosemide treated rats at dose of 10 mg/kg[26]. Hydro alcoholic leaf extract of *T. portulacastrum* also reported natriuretic effects in rat model[129].

Ethylene glycol is metabolised to glycolate by alcohol dehydrogenase, causing acidosis that precipitates crystal of calcium oxalate monohydratein. Renal, kidney injury, nervous system depression and cardiopulmonary failure is the cause of ethylene glycol poisoning[130,131]. The ethanolic extract of *T. portulacastrum* showed antilithiatic effect in ethylene glycol induced urolithiasis in male wistar rats at dose of 200 and 400 mg/kg b.w and found that urine output, phosphate, calcium, oxalate and magnesium level in urine, urea, creatinine and uric acid in blood level reestablished at near normal value after treatment[132].

Anti-inflammatory activities

Ethanolic extract of *T. portulacastrum* whole plant at dose of 100 mg/kg (*i.p.*) showed significant anti-inflammatory response against formaldehyde induced arthritis[120,133].

Antioxidant activities

T. portulacastrum extract showed free radical scavenging activity against hydrogen peroxide and DPPH (1,1-diphenyl-2-picryl hydrazyl)[134], ferric-reducing power and reversed the action of linoleic acid peroxidation activity[135]. Root extract showed greater inhibition effect against linoleic acid peroxidation compare to other parts[135]. Ethanolic extract of *T. portulacastrum* showed protection against radiation-induced oxidative damage in red blood cells membrane. It optimizes the radiation-induced elevated level of TBARS and inhibits ATPase activity in RBC membrane ghosts[136]. The presence of phenols, flavonoids and tannins, in particular, attenuates ROS[137].

Antihyperglycemic

Alloxan and streptozotocin are used to induce diabetes in animal through destruction of pancreatic B cell and DNA damage, respectively. Alloxan (2,4,5,6-tetraoxypyrimidine; 5,6-dioxyuracil)-induced diabetes has been commonly utilized as an animal model of insuln-independent diabetes mellitus. Alloxan and reduction product dialuric acid establish a redox cycle. Superoxide radicals, hydrogen peroxide and hydroxyl radicals are produced like a chain reaction. The action of ROS with a simultaneous massive increase in cytosolic calcium concentration causes rapid destruction of B cells[138].

Streptozotocin (STZ), an antibiotic with broad-spectrum activity, was isolated from a soil micro-organism Streptomyces achromogenes[139]. STZ has been widely used to generate an animal model of T1DM, because STZ-induced diabetes structurally, functionally, and biochemically resembles human T1DM[140,141]. Low affinity glucose transporter 2 (GLUT2) mediates the entry of STZ into the cells. It is known that GLUT2 is highly expressed in the liver, intestine, basolateral surface of kidney, pancreatic β-cells, and central nervous systems[142, 143]. Cells that express GLUT2 are sensitive to STZ[144]. STZ has diverse cytotoxic effects such as aberrant DNA alkylation, protein methylation and generation of reactive oxygen and nitrogen species (RONS)[145]. Excess RONS trigger cell death during early stages[146], impairs mitochondrial respiratory complex, inhibits aconitase activity, and transforms mitochondrial membrane potential, resulting in the disturbance in mitochondrial bioenergetics[147]. The pancreas is more vulnerable to oxidative stress than any other tissues because of the low level of antioxidant enzymes[145,148,149]. These effects of STZ are responsible

for necrosis of pancreatic β-cells[138]. Methanolic extract of *T. portulacastrum* whole plant yield anti-hyperglycemic activity against STZ (streptozotocin) induced diabetic rat[31], as well as alloxan stimulated hyperglycemic rat[117]. These results are comparable to oral hypoglycemic drug.

Hepatoprotective effects

The hepatoprotective activity of *T. portulacastrum* is maintained by regulation of immunity and erythropoiesis[150], antioxidant enzymatic activity[151].

Overdose (>4 g/day) of antipyretic drug paracetamol/ acetaminophen causes hepatotoxicity. Paracetamol excreted as glucoronide and sulphate conjugates through urine. Electrophilic intermediate N-acetyl-p-benzoquinone imine (NAPQI) formed by isoenzyme of cytochrome CYP2E1 is responsible for hepatotoxicity caused due to excess intake of paracetamol. Trace amount of NAPQI can be inactivated by glutathione, but excess amount of NAPQI deplete glutathione. Higher amount of NAPQI bind with hepatic protein covalently that causes cell death[152]. In nutshell, mechanism of liver injury (necrosis) is dependent on the accumulation of acetaminophen metabolites, NAPQI, NAPQI protein adducts, glutathione depletion, oxidative stress, and mitochondrial damage[153,154]. The inflammatory cytokines, such as TNF-α, IFN-γ, and IL-1β are also crucial for the development of acetaminophen hepatitis[155]. The NK and NKT cells play a detrimental role[156,157]. The underlying liver injury was mediated by production of IFN-γ, chemokines, and up-regulation of FasL expression in the liver[158]. Thioacetamide (TA) causes necrosis that lead to hepatotoxicity. Highly reactive thioacetamide S,S-dioxide ($TASO_2$) produced from intermediate thioacetamide S-oxide (TASO) formed by oxidative bioactivation of thioacetamide. $TASO_2$ alter protein structure and amine lipids causing hepatic damage[159]. TA also decreases the GSH level in hepatocyte that increases the ROS production including lipoperoxidation level, leading to mitochondrial injury and cell death[160]. Ethanolic leaf extract of *T. portulacastrum* demonstrated hepatoprotective activity against toxicity induced by thioacetamide and paracetamol[161] due to its antioxidant potential[162].

Carbon tetrachloride (CCl_4) is a potent hepatotoxin, induces acute and chronic hepatitis[163]. CCl_4 activates cytochromes (CYP2E1, CYP2B1 or CYP2B2) to form trichloromethyl (CCl_3) radical that reacts with oxygen to form a highly reactive oxygen species (ROS) CCl_3OO^* that initiate lipid peroxidation, denaturation of polyunsaturated fatty acids, mitochondria dependent liver injury and fatty degeneration[164]. As a result, the mitochondrial, endoplasmic reticulum and plasma membrane permeability is lost with deregulation of Ca^{2+} in the cells leading to cellular demise[164]. Additionally, CCl_4 toxicity leads to hypomethylation of cellular components and liver damage[164]. The increased influx of cytokines, chemokines and immune cells like neutrophils, following CCl_4-induced liver injury result in hepatocyte damage (necrosis)[165]. The Kupffer cells (KCs) also play a vital role in CCl_4-mediated hepatitis in mice as depletion of KCs protects CCl_4-induced liver necrosis and IL-6 production[166]. Another study demonstrated that CCl_4-mediated hepatitis was dependent upon the activity of KCs *via* TNF-α and FasL[167]. It causes fat degeneration and lipid accumulation in the liver causing loss of enzyme functions like glucose-6-phosphatases and cytochrome P-450 monooxygenase. CCl_4 is also responsible for reversible blocking of intracellular gap junction immediately after intoxication, leading to impaired movement of calcium and consequently cell death[168]. Ethanolic extract of *T. portulacastrum* showed protective effect against CCl_4 induced hepatotoxicity in mice[169]. This protective activity is comparable with the standard hepato-protective silymarin drug[170]. It showed protective effect on early DNA damage and chromosomal anomaly in mouse liver damaged by CCl_4[171]. Free radical scavenging activity and antioxidant property of ethanolic extract of *T. portulacastrum* reduces lipid peroxidation in CCl_4 induced mice model[151], as observed its hepatic destruction by histopathological, hematological and biochemical parameters in liver after oral administration of the *T. portulacastrum* extract on Swiss albino mice[150].

Aflatoxins (mycotoxins) are mostly produced by *Aspergillus flavus*, *Aspergillus parasiticus* and *Aspergillus nomius*[172]. Few other species of *Aspergillus* and *Emericella* are also reported to produce aflatoxins[173]. It has been reported that more than 18 different types of aflatoxins occur in nature, among them B1, B2, G1 and G2 mostly affect animals and humans. These aflatoxins cause toxic effects leading to mutagenicity, carcinogenicity and hepatotoxicity[174]. Aflatoxin B1 (AFB1) has been considered to be more toxic than other aflatoxins[174]. The liver is a primary target for AFB1, along with the heart, kidney, lungs, testis and bone marrow[174].

Orally treated AFB1 is absorbed in the small intestines and metabolised in the liver. In the liver, AFB1 is biotransformed by microsomal cytochrome

P450 to a highly reactive intermediate, AFB1-8, 9-epoxide, which binds to nucleic acids to form adducts[175]. These adducts could block transcription and translation, thereby affecting the regulation of functional gene expression and ultimately causing hepatotoxicity[175]. AFB1-induced hepatotoxicity also results from accumulation of ROS, interact with DNA and lead to mutations[175]. Acute aflatoxicosis resulting from exposure to high doses of AFB1 through the diet over a short period causes hepatotoxicity while chronic aflatoxicosis resulting from exposure to low doses of AFB1 through the diet over a long period of time has been implicated in hepatocellular carcinoma[176].

Caspases are critical mediators of apoptotic cell death where caspase-3 is activated by mitochondria-dependent (intrinsic) and independent (extrinsic) cell death pathways[177]. Bax, a pro-apoptotic protein induces the transport of cytochrome c from the outer membrane of mitochondrial to the cytosol, and the anti-apoptotic protein Bcl-2 is involved in releasing cytochrome c[178]. AFB1 was included in the 1st class human carcinogen group by the International Agency for Research on Cancer in 1993[179]. Pretreatment of mouse with ethanolic leaves extract of *T. portulacastrum* (administered orally) showed aflatoxin B1 (AFB1, a hepatocarcinogenic) stimulated hepatotoxicity[180]. Another study showed that administration of extract at dose 50-800 mg/kg four times in 3 h interval exerted hepatoprotection[181].

Methanolic extract of *T. portulacastrum* reduced lipid and cholesterol level in serum and protected against hepatocellular damage induced by atherosclerotic diet (0.5% thiouracil, 1% cholic acid and 4% cholesterol) observed in rat[128].

Antioxidant and Protective Mechanism

A basal level of activity by these defensive systems of cells appears to be sufficient to protect cells against various oxidative stresses under normal conditions. Redox-responsive transcription factor, Nrf2 is the chief regulator of cellular homeostasis. Nrf2 mediates the expression of numerous oxidative stress related genes, including antioxidant proteins, phase I and II detoxification enzymes, transport proteins, proteasome subunits, chaperones, growth factors and their receptors, and some transcription factors[182-184].

Under basal conditions, Nrf2 is primarily regulated by the Kelch-like ECH-associated protein1 (Keap1), an adaptor protein of the Cullin3 (Cul3) based E3-ligase. This Cul3-E3 ubiquitin ligase complex mediates the proteasomal degradation of Nrf2. Under normal physiological conditions, Keap1 constitutively targets Nrf2 for ubiquitin-dependent proteasomal degradation. Keap1 is inactivated during oxidative stress, and the ubiquitination of Nrf2 stops, which leads to conformational changes in the Nrf2-Keap1-Cul3 complex, and activate Nrf2. Activated Nrf2 translocate into the nucleus and binds to the antioxidant response element (ARE) located in the promoter region of Nrf2 target genes. Consequently, it induces the transcription of cytoprotective genes, leading to the activation of the defensive system[185, 186]. Nrf2 is primarily expressed in metabolically active organs such as the liver[187]. The phytochemicals present in fruits and vegetables have been shown to specifically react with the cysteine residues of Keap1 leading to a conformational change, which results in diminished tagging of Nrf2 for proteolysis. Thus, phytochemicals from *T. portulacastrum* activated Nrf2, which might be beneficial in protecting against liver injury[188-190].

Anticarcinogenic activity

Diethylnitrosamine (DENA) is a carcinogenic agent and plays an important role in cell cycle regulation. DENA induces hepatocellular carcinoma (HCC) through over expression of regulatory protein of G_1/S phase in rat[191]. It has been proposed that DENA-induced HCC in mice models has closer histologic and genetic features to those observed in human HCC of poor prognosis than others HCC models[192]. DENA is biotransformed by cytochrome P450 enzymes into an ethyldiazonium ion, an electrophile that forms DENA-DNA adducts, with concomitant release of ROS[193-195]. Both oxidative stress and DNA adduct formation contribute to DENA carcinogenicity. *T. portulacastrum* extract showed chemo preventive activity in Sprague–Dawley rat model exposed by DENA[196]. Chloroform extract also exhibited protection against hepatocarcinogenesis initiated by DENA and Phenobarbital[197].

7,12-dimethylbenz[a]anthracene or DMBA, a polycyclic aromatic hydrocarbon, is one of the major carcinogenic components of car and industrial exhaust and char-broiled food[198]. It initiates and promotes tumorigenesis, especially in the breast, ovary and skin depending on the route of exposure[199]. It has been reported that DMBA activates the aryl hydrocarbon receptor (AhR) transcription factor that regulates a number of genes involved in cellular metabolism[200]. AhR upregulate the cytochrome P450 enzymes and

metabolizes DMBA into a mutagenic intermediate that causes DNA damage and is responsible for the initiation of tumorigenesis[201,202]. DMBA up regulate the expression of Cyclin D1 and c-Myc, possibly through NF-κB and Wnt pathways, and play critical role in carcinogenesis[203]. Ethanolic extract of *T. portulacastrum* showed chemopreventive activity against DMBA-induced tumorigenic mammary gland in female Sprague-Dawley rats[204].

Oxidative stress and Microenvironment in Cancer

Oxidative stress is involved in different stages of carcinogenesis; initiation, promotion and progression. Free radicals activate numerous mechanisms at the initiation step and contributing to mutations. In the promotion step initiated cells either enhances the proliferation and/or inhibits the cell death. During the progression step, free radicals cause uncontrolled growth of tumor cells, resistance to chemotherapy, genomic instability, metastasis and invasion[205]. Antioxidants from phytochemicals, such as *T. portulacastrum*, detoxify free radicals and ROS directly or indirectly, and thus may protect against cancer[206].

Conclusion

Trianthema portulacastrum L. has shown its potential as nutritional plant as well for the remedial purposes in different medical purposes, such as inflammation, microbial infection, antioxidant, hyperglycemia, nephropathy and cancer *etc*. The phytochemicals present in *T. portulacastrum* are responsible for health benefits. Available evidences suggest that antioxidant property of this plant is one of the major factors responsible for its beneficial effects. On the contrary, understanding of the detailed protective mechanisms in several medical conditions is yet to be elucidated. Extensive study on the available phytochemicals from *T. portulacastrum* and elucidation of their mechanism on action will help to develop new drug(s) in several ailment conditions at a low cost due to its abundant availability.

Acknowledgement

Financial assistance received from DAE-BRNS (no. 35/14/39/2016-BRNS) is greatly acknowledged.

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