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Preclinical activities of *Cassia tora* Linn against aging-related diseases

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Abstract

Globally, an aging population is increasing, and aging is a natural physiological process and a major risk factor for all age-related diseases. It seriously threatens personal health and imposes a great economic burden. Therefore, there is a growing scientific interest in strategies for well-aging with prevention and treatment of age-related diseases. The seed, root, stem or leaves of *Cassia tora* Linn. are useful for anti-bacteria, anti-hyperlipidemia and anti-obesity due to its pharmacological activities such as anti-inflammation and anti-oxidant both in vitro and in vivo. Nevertheless, no clinical trials have been attempted so far, therefore here we would like to understand the current preclinical activities for aging-related disease models including cataract, metabolic dysfunction and neurodegeneration, then discuss their preparation for clinical trials and perspectives.

Introduction

According to the United Nations report, the global population of over sixty-five years old is expected to increase every year (Ref. 1). The aging process increases the incidence and prevalence of age-related disorders in organs such as the eyes, intestines and brain, due to physiological factors. The main cause of aging-related diseases is an increase in intracellular inflammatory and immune response, which are highly correlated with an increase in oxidative stress. That is, oxidative stress induces the expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κ B), interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF) α, cyclooxygenase (COX)-2, and inducible NO synthase to cause an inflammatory response, which can cause to cataracts, metabolic diseases, Alzheimer's disease, dementia, etc (Ref. 2) (Fig. 1). Thus, it is growing interest to treat or prevent the age-related diseases.

Phytomedicine is an herbal extract which is derived from a plant in whole or in part. It is generally more meaningful in the current medical system as it is a useful cause of an advantage over synthetic compounds in toxicity, and new interest has been established in finding the relationship between herbal extracts and disease prevention (Refs 3–5).

Cassia tora Linn. (*C. tora*) is an annual plant involved in Fabaceae family and grows in Asia including, China, India and Nepal (Refs 6, 7) and its seed commonly drinks as a tea. Extracts from leaves and seed parts are using for medicinal activities such as anti-allergic, anti-asthenic, anti-oxidant, anti-hepatotoxic, anti-diabetic and anti-mutagenic (Refs 6–8). The cream containing *C. tora* improved the ultraviolet-induced psoriasis in rats (Ref. 9). Sushant Aryal *et al.*, investigated the anti-oxidant potential activities of *C. tora* with IC_{50} = 9.898 µg/ml of DPPH radical scavenging activity and IC_{50} = 22.52 µg/ml of hydroxyperoxide scavenging activity (Ref. 10). Latestly, Khalifa Sam *et al.*, screened the natural extracts or components for treatment of coronavirus infections, and *C. tora* was listed as a candidate for preclinical and clinical study (Ref. 11). According to the different extraction solvents including acetonitrile, ethylacetate, 70% or 90% of ethanol and methanol, and parts of *C. tora*, such as root, leaves, stems and seeds, the major components are different like rotenoids, anthraquinones, naphthopyran glycosides naphthalene glycoside and ononitols (Refs 12–15).

Effects of *Cassia tora* L. on aging-related diseases

Cataract

Vision is important throughout life, however as we age, functional impairments, including cataracts with clouding of the lens, can be appeared by oxidative stress, one of the major factors. Ethyl acetate extracts of *C. tora* leaves showed antioxidant effects on selenite-induced cataract rat model (Ref. 16). The extracts decreased activities of myeloperoxidase and calpain which are catalyzer of reactive oxidant species (ROS) formation and increased activities of superoxide dismutase and catalase which are scavenger of ROS production. Also, selenite-induced lens damage was prevented by upregulation of cytochrome C oxidase 1 activity and ATP level as well as ubiquitin-activating enzyme (Ube)1 and Ube2 expression (Ref. 16). Meanwhile ethyl

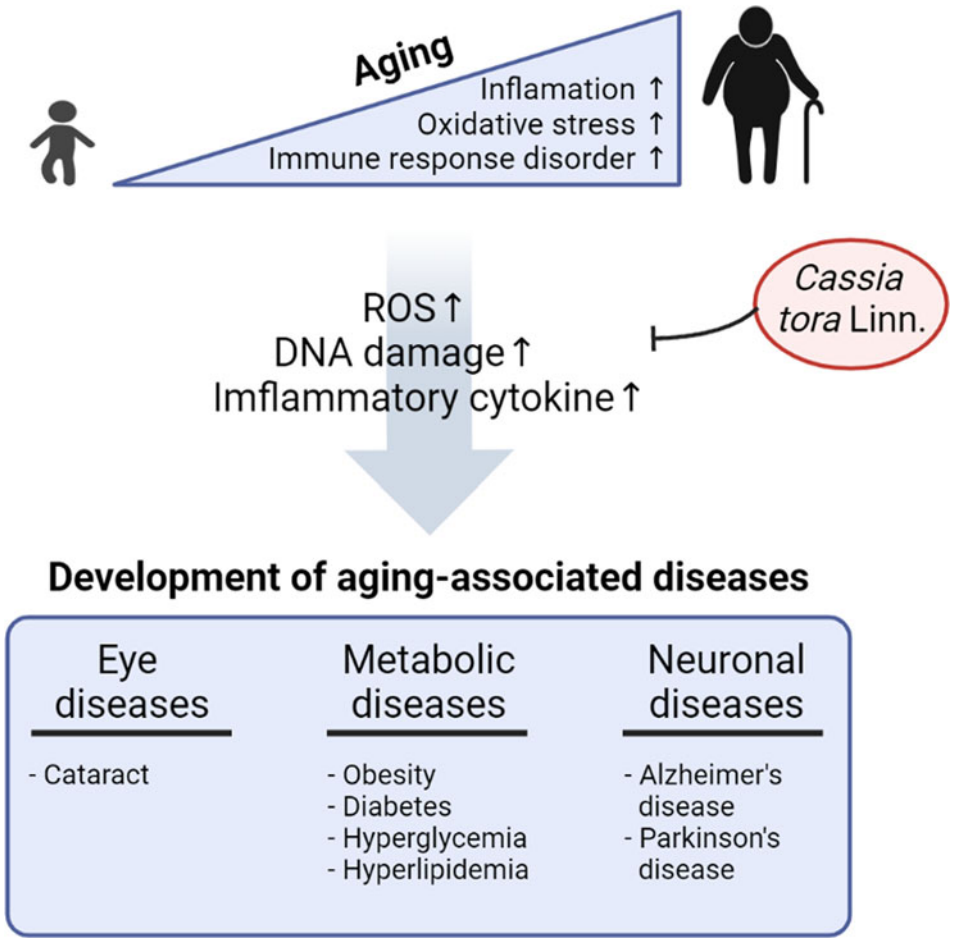

Fig. 1. An illustration of link between aging-related diseases and *Cassia tora* L. Aging changes pathological phenomena by induction of oxidative stresses and inflammatory responses thus causes to aging-related diseases including cataract, metabolic disease and neuronal disease, and *Cassia tora* Linn improves the diseases.

acetate extracts of *C. tora* leaves including chrysophanol, emodin, kaemferol, quercetin, stigmasterol and isoquercetin reduced mRNA level of NFκB and early growth response protein (Egr)-1, and induced activities of superoxide dismutase, catalase and Na^+ K^+-ATPase thus inhibited selenite-induced cataractogenesis in rat pups (Ref. 12). It might be caused by acetate extracts enhanced reduced-glutathione level, and gamma glutamylcysteine synthase, glutathione peroxidase, glutathione reductase and glutathione-S-transferase activities (Ref. 17) (Figs 1 and 2, Table 1).

Metabolic disease

According to the development of economics and expended life-span, patients with metabolic dysfunctions such as obesity and diabetes are emerged and increased. It is closely related with inflammation and immune responses as well as oxidative stresses (Ref. 18).

Ethanol (70%) extracts of *C. tora* seed ameliorated high fat diet (HFD)-induced obesity and -hyperlipidemia as well as -insulin resistance and secretion in mice model. Because hyperinsulinemia induced mitochondrial dysfunction in pancreas, treatment of ethanol extracts recovered the mitochondrial biogenesis of pancreas by increasing mitochondrial complexes expression and activity. It means that ethanol extracts of *C. tora* seed will be useful for treatment of type2 diabetes metabolic disease (Ref. 15).

Ononitol monohydrate, a kind of glycoside form extracted from *C. tora* leaves inhibited lipid accumulation and adipocyte maturation by enhancing mitochondrial membrane potential (Ref. 13). In the adipogenic factors which are inflammatory mediators, adiponectin level was increased, and leptin, CCAAT/enhancer binding protein α and leukotriene B4 Receptor (LTB4R) levels were decreased. Ononitol monohydrate induced the expression of uncoupling protein-1, PR/SET domain 16, peroxisome proliferator activated receptor gamma coactivator 1 alpha and sterol-regulatory element binding protein-1C for adipocyte browning. Moreover, ononitol monohydrate suppressed signal transducer and activator of transcription (STAT) 6 and LTB4R expression which are involved in insulin resistance of adipocytes.

Ethanol (90%) extracts of *C. tora* seeds in a dose of 500 mg/kg reduced plasma and liver level of total cholesterol, phospholipids and triglyceride and induced post heparin lipolytic and lipoprotein lipase activity in both triton WR-1339-medicated acute and cholesterol rich HFD- induced hyperlipidemia rat model (Ref. 19)

Ethanol (95%) extracts of *C. tora* seeds with orally administration of 500 mg/kg down-regulated levels of blood glucose, total cholesterol, phospholipid, triglyceride and free fatty acid and up-regulated post-heparin lipolytic activity (Ref. 20). In addition, ethanol extracts inhibited oxygen free radicals such as O_2^- anions and OH^- radical by extracts treatment of 400 mg/kg, in vivo.

Anthraquinone and naphthalene derivatives containing 7-methoxy-obtusifolin, aurantio-obtusin, chrysoobtusin, obtusin, obtusifolin, emodin, physcion, chrysophanol, cassiaside, rubrofusarin-6-O-gentiobiosideol, obtusifolin-2-glucoside, chryso-obtusin-2-O-glucoside, cassitoroside, toralactone-9-O-gentiobioside, physcion-8-O-gentiobioside and glucoaurantio-obtusin from ethyl acetate and butanol fractions of *C. tora* seed significantly inhibited soluble epoxide hydrolase activity which is a key lipid mediator for vasodilatation, blood pressure regulation and heart dysfunction (Ref. 21) (Figs 1 and 2, Tables 1 and 2).

Neuronal disease

As an aging society, neurodegeneration disease decreases the quality of life. Neurodegenerative disorders such as Alzheimer's

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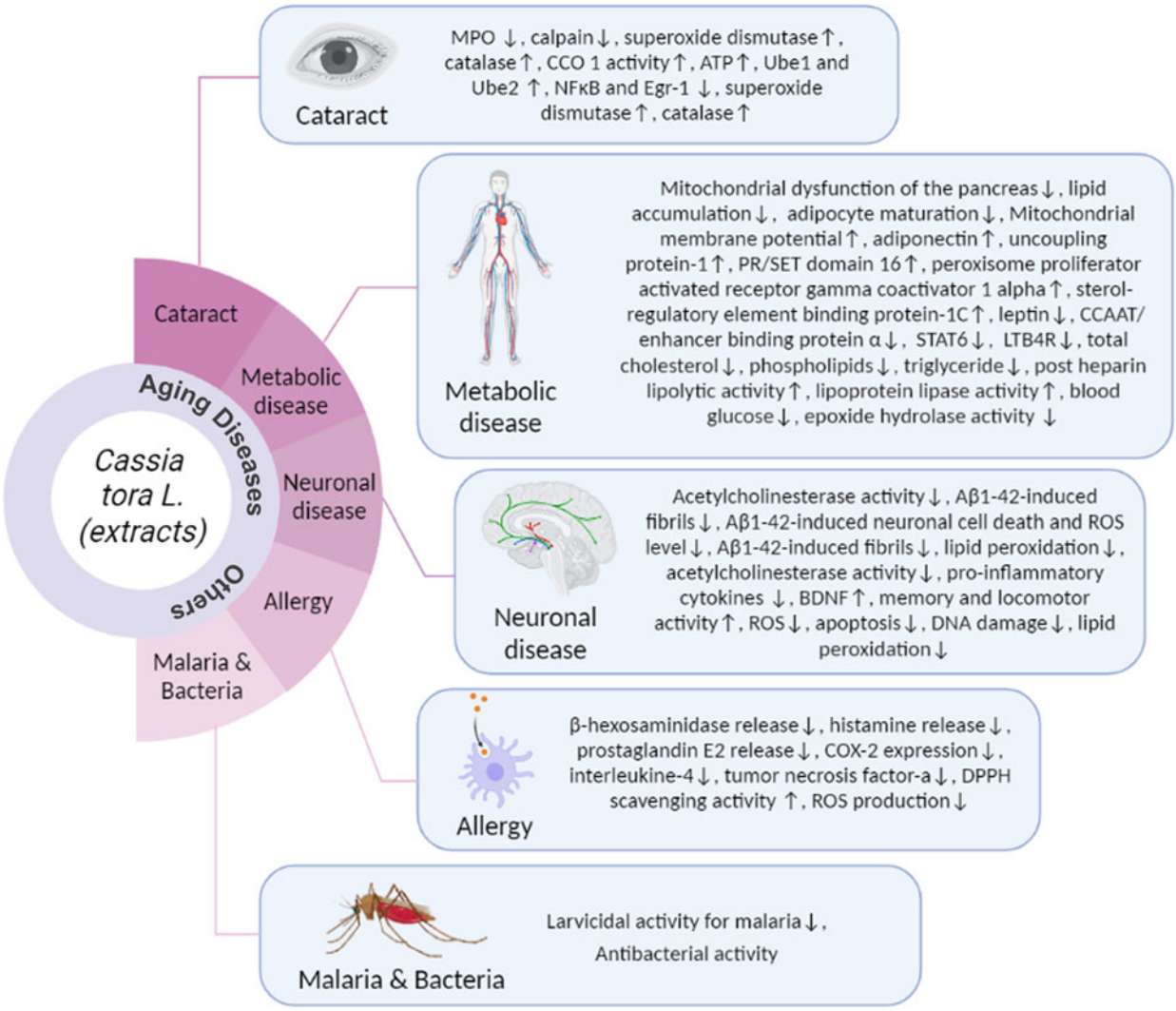

Fig. 2. Therapeutic effects of *Cassia tora* L. on aging-related diseases. *Cassia tora* L. exhibits pharmacological activities for anti-cataract, anti-metabolic disease, anti-neuronal disease and others including anti-malaria, anti-bacterial, and anti-allergy by depletion of oxidative stresses and inflammatory factors. MPO, myeloperoxidase; CCO 1, cytochrome c oxidase 1; ATP, adenosine triphosphate; Ube, ubiquitin-activating enzyme; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; Egr-1, early growth response protein 1; STAT6, signal transducer and activator of transcription 6; LTB4R, Leukotriene B4 Receptor; BDNF, brain derived neurotrophic factor; ROS, reactive oxygen species; COX-2, cyclooxygenase-2; DPPH, 2,2-diphenyl-1-picrylhydrazyl.

disease and Parkinson's disease are unavoidable progressions caused by oxidative damage, mitochondrial dysfunction, bioenergetic changes and neuroinflammatory responses (Ref. 22).

Ethyl acetate extracts of *C. tora* leaves inhibited acetylcholinesterase activity and fibrillations in vitro in doses of 20–100 μg/ml and 25 or 50 μg/ml (Ref. 23). In human neuroblastoma cells, SH-SY5Y and SK-N-SH, ethyl acetate extracts rescued the cell viability from the $A\beta_{1-42}$-mediated cell death and prevented the ROS production at 50 and 100 μg/ml (Ref. 23).

Chethana K. R reported that methanol fraction among methanol, n-hexane, petroleum ether and aqueous extracts from *C. tora* leaves exhibited inhibitory effects on acetylcholinesterase and butyralycholinesterase activities and fibrillation (Ref. 24).

Methanol extracts from *C. tora* leaves containing mainly flavonoids such as quercetin, rutin and kaempferol, and minorly phenolic compounds such as vanillic acid, gallic acid, p-coumaric acid and ferulic acid inhibited $A\beta_{1-42}$ aggregates formation of monomer, oligomer and fibril by quantifying of thioflavin-T assay in vitro at 100 μg/ml (Ref. 25), and reduced the time of escape latency, northwestern latency and time spent in the target quadrant and induced the number of crosses of the original platform location by analysis of Morris water maze tests in aluminium-induced Alzheimer's disease rat model at 100 or 400 mg/kg, daily for 60 days. Also, methanol extracts restored the locomoter and exploratory activities. Furthermore, it was recovered antioxidant enzyme activity such as catalase, glutathione peroxidatse and glutathione S-transferase and inhibited lipid peroxidation as well as acetylcholinesterase activity in hippocampus and frontal cortex. In the underlying mechanism, methanol extracts decreased the expression of inflammatory cytokines such as interleukin (IL)-1β, IL-6, TNF-α and increased brain-derived neurotrophic factor (BDNF) (Ref. 25).

Ethyl acetate or methanol extracts from *C. tora* leaves induced DPPH scavenging activity and reduced paraquat-induced Parkinson's disease cell model via inhibiting ROS production, cell death, DNA damage and lipid peroxidation (malanoldehyde formation) (Ref. 26) (Figs 1 and 2, Table 1).

Effects of *Cassia tora* L. on other diseases

Allergy

Allergy in the immune system is an acquired hypersensitivity response to external stimuli and substances, which can cause allergic asthma, conjunctivitis, rhinitis, urticaria, etc. Remarkably, mast cells show an important role in triggering immunoglobulin E

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Table 1. Preclinical activities of *Cassia tora* L

Components and sources	Activities	Model	Reference
Ethyl acetate fraction of leaves	myeloperoxidase (MPO) ↓ calpain↓ superoxide dismutase↑ catalase↑ Cytochrome C oxidase 1 (CCO 1) activity↑ ATP↑ Ube1 and Ube2 ↑	Selenite-induced cataract rat model (p.o., 5 μg/g, 30 days)	(Ref. 16)
Ethyl acetate fraction of leaves	NFκB and Egr-1 ↓ superoxide dismutase↑ catalase↑	selenite induced cataractogenesis in rat pups	(Ref. 12)
Ethanol (70%) extracts from seed	Mitochondrial dysfunction of the pancreas↓	High fat diet (HFD) mouse model (0.1% Cassia tora seed extracts, 12 weeks)	(Ref. 15)
Ononitol monohydrate of leaves	lipid accumulation↓, adipocyte maturation↓, Mitochondrial membrane potential↑ adiponectin↑, uncoupling protein-1↑, PR/SET domain 16↑, peroxisome proliferator activated receptor gamma coactivator 1 alpha↑, sterol-regulatory element binding protein-1C↑, leptin↓, CCAAT/enhancer binding protein α↓, STAT6↓, LTB4R↓	Adipocyte differentiation factors-induced immortalised human bone marrow mesenchymal stem (hMSC) cell model	(Ref. 13)
Ethanol (90%) extract from seeds	total cholesterol↓, phospholipids↓, triglyceride↓, post heparin lipolytic activity↑, lipoprotein lipase activity↑	Triton- and cholesterol rich-HFD- induced hyperlipidemia rat model; p.o., 500 and 200 mg/kg	(Ref. 19)
Ethanol (95%) extracts of seeds	blood glucose↓, total cholesterol↓, phospholipid↓, triglyceride↓, free fatty acid↓, post-heparin lipolytic activity↑	Streptozotocin-induced hyperglycaemia in Charles foster rat model (p.o., 500 mg/kg, 15 days)	(Ref. 20)
ethyl acetate and butanol fractions from seed	epoxide hydrolase activity ↓	In vitro	(Ref. 21)
Ethyl acetate extract of leaf	Acetylcholinesterase activity↓ Aβ_{1-42}-induced fibrils↓, Aβ_{1-42}-induced neuronal cell death and ROS level↓	human neuroblastoma cells	(Ref. 23)
Methanol extract of leaf	Aβ_{1-42}-induced fibrils↓, lipid peroxidation↓, acetylcholinesterase activity↓, pro-inflammatory cytokines ↓, BDNF↑, memory and locomotor activity↑	Aluminium-induced neuronal disease rat model (daily ingestion of 100 and 400 mg/kg, 60 days)	(Ref. 25)
Ethyl acetate or methanol extracts from Cassia tora leaves	ROS↓, apoptosis↓, DNA damage↓ lipid peroxidation↓	paraquat-induced Parkinson's disease cell model (human neuroblatoma SK-N-SH)	(Ref. 26)
Ethanol (95%) extracts from seeds	β-hexosaminidase release↓, histamine release↓, prostaglandin E2 release↓, COX-2 expression↓	Antidinitrophenyl-IgE-sensitised RBL-2H3 cells, IgE-induced passive cutaneous anaphylaxis mouse model (p.o., 200 mg/kg for extract, 50 mg/kg for aurantio-obtusin)	(Ref. 27)
AF-343, a hot-water extraction mixture of *Cassia tora* L., *Ulmus pumila*, L. and *Taraxacum officinale*	β-hexosaminidase release↓, interleukine-4↓, TNF-a↓, DPPH scavenging activity ↑, ROS production↓	Compound 48/80-induced allergic response RBL-2H3 cells	(Ref. 28)
Rotenoids from root	Larvicidal activity for malaria (LC50-120.61 ppm)↓	late third/early fourth instar larvae of A. *stephensi*	(Ref. 14)
Fatty acid methyl ester fractions from leaves and stem	Antibacterial activity	Microdilution in vitro assay against methicillin-resistant staphylococcus aureus, methicillin-sensitive staphylococcus aureus, bacillus subtilis and pseudomonas aeruginosa	(Ref. 30)

Table 2. Components from different solvents and parts of *Cassia tora*

Extracts solvents	Parts of	Components	References
ethyl acetate and butanol	*C. tora* seed	anthraquinone and naphthalene derivatives	(Ref. 21)
Methanol	*C. tora* leaves	enriched flavonoids such as quercetin, rutin, kaempferol and phenolic compounds such as vanillic acid, gallic acid, p-counaric acid, ferulic acid	(Ref. 25)
Ethanol (70%)	*C. tora* seeds	rhein, emodin and chrysophanol	(Ref. 15)
Ethanol (95%)	*C. tora* seeds	gluco-aurantioobtusin, gluco-obtusifolin, aurantio-obtusin, chryso-obtusin, obtusin and obtusifolin	(Ref. 27)

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(IgE)-mediated allergic reactions and its activation can be induced by interaction of allergen-IgE linked with high-affinity IgE receptor thus release inflammatory cytokines (Ref. 22).

Ethanol (95%) extracts (5, 10 or 20 μg/ml) from *C. tora* seeds extracts containing gluco-aurantioobtusin, gluco-obtusifolin, aurantio-obtusin, chryso-obtusin, obtusin and obtusifolin inhibited secretion of histamine, β-hexosaminidase (degranulation marker) and prostaglanding E2 (inflammatory arachidonic pathway product), and COX-2 expression and reactive oxygen species production in antidinitrophenyl-IgE-sensitised RBL-2H3 cells and dinitrophenyl-IgE-induced passive cutaneous anaphylaxis mouse in vivo (Ref. 27). The inflammatory cytokines level such as TNF-α and interleukin-4 was decreased following the reduction of high-affinity receptor mediated cascades for the Fc region of Ig E. Furthermore, it was identified that aurantio-obtusin is the most active and major fraction component among the six compounds of extracts, and the activity of aurantio-obtusin at 20 μM was shown to clearly similar tendency in the above pharmacological examinations (Ref. 27).

AF-343, a hot-water extraction mixture of *Cassia tora* L., *Ulmus pumila*, L., and *Taraxacum officinale*, and each mixture inhibited compound 48/80-induced degranulation and inflammation in RBL-2H3 cells by measuring β-hexosaminidase release and inflammatory cytokine production such as interleukine-4 and TNF-α (Ref. 28). While AF-343 and each mixture induced 1,1-diphenyl-2picrylhydrazyl (DPPH) scavenging activity and reduced ROS production in compound 48/80-induced oxidative stresses of RBL-2H3 cells (Fig. 2, Table 1).

Malaria

Malaria which can be severe to death, is caused by the Plasmodium parasite, and infected female Anopheles mosquito transmitted to people by biting. P. *falciparum* and P. *vivax* are the most threat and prevalent on African continent and countries outside of sub-Saharan Africa (Ref. 29). Rotenoids containing sumatrol, rotenone, tephrosin, rotenol, deguelin and elliptone were extracted from *C. tora* root under acetonitrile saturated with n-hexane and showed anti-larvicidal activity with LC_{50} = 120.61 ppm to larvae of A. *stephensi* (Ref. 14). While fatty acid methyl ester fractions from *C. tora* leaves and stem inhibited the bacteria activities including methicillin-resistant staphylococcus aureus, methicillin-sensitive staphylococcus aureus and bacillus subtilis (gram-positive) and pseudomonas aeruginosa (gram-negative) (Ref. 30). Ethyl acetate extracts which contained major active components aurantio-obtusin and obtusin from *C. tora* seed inhibited mosquito larvicidal activity to LD_{50} = 2.5 ppm (Ref. 31). (Fig. 2, Table 1)

Discussion and perspectives

From the querying in Pubmed for *Cassia tora*, the publications are only 120 although its high potential activities for anti-oxidants and anti-inflammation. With recent five years' publication, we found the major target diseases of *Cassia tora* Linn., such as cataract, obesity, diabetes, Alzheimer's disease, and Parkin's disease in vitro and in vivo preclinical studies which are highly related with aging-disease. Others were allergy, malaria and bacteria. For extending the clinical study, we may consider the toxicity. From the quantitative structure activity relationship study for hepato- and nephrotoxicity, chryso-obtusin, 1,7,8-methoxyl-2-hydroxyl-3-methyl-anthraquinone and chryso-obtusin-2-β-D-glucoside was supposed hepatotoxicity and 1,7,8-methoxyl-2-hydroxyl-3-methyl-anthraquinone, emodin, chrysophanol, aloe-emodin, rhein, rhein-8-O-β-D-glucoside, obtusifoline-2-O-β-D-glucoside and 9,10-anthracenedione were expected nephrotoxicity, and triptolide, a positive control, were showed renal and hepatic cytotoxicity (Ref. 32). Especially emodin showed the IC_{50} = 139.90 μM or 88.97 μM of cytotoxicity in HK-2 normal kidney cells with single culture or co-culture, respectively and hepatoxicity in rat with 500 mg/kg orally by induction of CYP3A and depletion of GSH levels (Refs 32, 33). While ethanol extracts from *C. tora* seeds also was evaluated no toxicity in rat with oral administration of 500, 1000 and 2000 mg/kg/day for 13 weeks (Ref. 34).

Additionally, more preclinical evidences are required such as pharmacokinetic and pharmacodynamic analysis based on the standardisation of extraction methods, and efforts are needed to modification of formulation for improving the solubility. Then it could be successfully applied for the prevention and therapy of aging-related diseases.

Search strategy and selection criteria

This review was prepared by searching in PubMed with the query key words: Cassia tora and Cassia tora Linn. The search was conducted for research articles including in vitro and in vivo preclinical reports, up to 15 June 2022 within the past five years.

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Authors' contribution. SYH, CSN and BCM contributed to the literature search and collection of articles, assisted with designing the figures and writing; MHL and JHS designed the structure of manuscript, edited the manuscript, supervised the studies and allocated the funding.

Conflicts of interests. No potential conflicts of interest are disclosed.

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