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Mast Cell Stabilizing Potential of Plants Containing Polyphenols: A Review.

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ABSTRACT

Mast cells play a vital role in the defence of the human body. Mast cell degranulation has been implicated in various ailments including allergies, bronchial asthma, interstitial cystitis, breast cancer, urticaria, etc. Hence mast cell stabilizers play a significant role in the prevention of these disorders. The primary objective of this review is to study the reports on different plants containing polyphenols with significant mast cell stabilizing activity. It includes findings from numerous studies both in vitro and in vivo indicating the potential benefits of polyphenol rich plants in mast cell stabilization. Various databases such as Pubmed, Google Scholar, Science direct, etc. were searched to collect reports on plants containing polyphenols investigated as mast cell stabilizers from the time period 1995-2015. The large number of plants described in this review clearly demonstrated the importance of polyphenol-rich plants in the mast cell stabilization. Literature shows that such plants significantly prevent mast cell degranulation by diverse mechanisms including inhibiting histamine release, reducing production of mediators of inflammation and antioxidant activity in various allergic/immune reactions in experimental models. Plants containing polyphenols/plant-derived polyphenols may serve as good sources for developing effective and safe mast cell stabilizers.

Keywords: Mastocytes stability, degranulation prevention, natural phenolic compounds

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INTRODUCTION

Mast cells or mastocytes are large connective tissue cells, originated from a distinct precursor in the bone marrow called hematopoietic progenitor cells. These play a pivotal role in defense mechanisms of human body [1]. They are residents of several types of tissues specifically in the vicinity of blood vessels, and are prominent near the boundaries between the outside world and the internal environment, such as the skin, mucosa of the lungs and digestive tract, as well as in the mouth, conjunctiva and nose [2]. They are activated through antigen cross linking of their surface receptors (FcεRI) for IgE antibodies leading to degranulation and the release of vasoactive, and pro-inflammatory mediators that include histamine, cytokines and proteolytic enzymes [3,4].

Mast cells are involved in variety of ailments such as different types of allergic and inflammatory reactions, atopic dermatitis, asthma, ulcers, psoriasis, obesity, interstitial cystitis, cancer etc [5]. Hence, mast cell stabilizers hold significance in the management of such disorders. They block calcium channels essential for mast cell degranulation, thus stabilizing the cell and thereby preventing release of several mediators. They are classified as chromone-like drugs (disodium cromoglycate, nedocromil sodium) and dual-action antihistaminics (ketotifen, azelastine, second-generation H1-receptor antagonists: cetirizine, loratidine). Several adverse effects associated with these drugs are bronchospasm, wheezing, angiodema, eosinophilic infiltration, anaphylaxis, joint swelling, pain and headache, drowsiness, lethargy, dryness of mouth, etc.

Need for plants as source of mast cell stabilizers

Despite the relative success of the most commonly prescribed mast cell stabilizer, disodium cromoglycate, ketotifen, etc. there still remains an urgent need to design new substances that are economical and relatively safer with fewer adverse effects. One of the most established mast cell stabilizer - disodium cromoglycate (DSCG) was first synthesized from a plant chromone – Khellin, present in Ammi visnaga by Roger Altounyan and his colleagues in 1965 [6]. Thus medicinal plants are currently being explored widely for finding new mast cell stabilizers. Plants provide us with several phytoconstituents e.g. simple phenols, coumarins, flavonoids, alkaloids, terpenoids, etc. that have demonstrated potent mast cell stabilizing potential in experimental models [7].

METHODS

Various databases such as Pubmed, Google Scholar, Science direct, etc. were searched to collect reports on plants containing polyphenols investigated as mast cell. The present review summarizes various studies, both in vitro and in vivo, conducted in the time period from 1995 to 2014 on different plants containing polyphenols for mast cell stabilizing activity (Table 1).

Table 1: Role of plants containing polyphenols in mast cell stabilization

Plant	Extract/ Constituent	Model	Dose	Observations	Reference
Abrus precatorius L. (Fabaceae)	Ethanolic extract	*In-vivo*: Egg albumin induced mast cell degranulation in mice and PCA reaction in rats.	100-150 mg/kg, i.p.	Significantly protect degranulation of mast cell and inhibit area of leakage of dye in passive cutaneous anaphylaxis. LD50 is more than 1300 mg/kg.	[24]
Acanthopanax senticosus (Rupr. & Maxim.) Harms (Araliaceae)	Aqueous extract	*In-vitro*: Compound 48/80 induced RPMC.	0.01 to 2.0 g/l	Dose dependent inhibition of histamine release.	[25]
		In-vivo: PCA reaction induced by anti-dinitrophenyl IgE.	2.0 g/kg	Inhibition of PCA reaction significantly.	
		In-vivo:	1 g/kg	25% inhibition of systemic	[26]

		Compound 48/80 induced systemic allergy.		allergy and 51% inhibition of PCA reaction.	
Aegle marmelos (L.) Corrêa (Rutaceae)	Unripe fruit extract	*In-vivo*: Acetic acid induced ulcerative colitis and indomethacin-induced enterocolitis in Wistar albino rats.	150, 200 and 250 mg/kg	Anti-inflammatory, antioxidant, and mast cell stabilizing effects in inflammatory bowel disease.	[27]
Ailanthus excelsa Roxb. (Simaroubaceae)	Methanolic extract	*In-vivo*: Clonidine induced mast cell degranulation.	100, 200 and 400 mg/kg	Dose dependent inhibition of mast cell degranulation.	[28]
Albezzia lebbeck (L.) Benth. (Fabaceae)	Successive chloroform, methanol and water extracts of bark and leaves	*In-vitro*: compound 48/80 induced reaction	-	Methanolic extract showed significant mast cell stabilizing activity	[29]
	Ethanolic extract	*In-vivo*: Ag-IgE Activated mast cells.	50-300 mg/kg	Significant mast cell stabilisizing potential with IC50 of 85 µg/ml.	[30]
Allium cepa L. (Amaryllidaceae)	A herbal fraction (ALC-02)	*In-vitro*: Compound 48/80-induced RPMC and systemic anaphylaxis reaction.	-	Potent inhibition of histamine release both *in-vitro* and *in-vivo* from sensitized mast cells.	[31]
Ammomum xanthiodes Roxb. (Zingiberaceae)	Aqueous extract	*In-vivo*: Compound 48/80-induced systemic reactions and serum histamine release in mice.	0.005–1 g/kg	Reduce mast cell mediated allergic reactions by significantly reducing histamine release and intracellular calcium.	[32]
Aristolochia bracteolate (Aristolochiaceae)	Chloroform extract	*In-vivo*: Compound 48/80 induced RPMC.	100, 200, 400, 500 mg/kg orally	Reduce the number of activated mast cells dose dependently.	[33]
		In-vivo: Compound 48/80 induced systemic anaphylaxis in mice.	100,200, 400,500 mg/kg orally	Dose dependent inhibition of mortality in mice.	
Artemisia iwayomogi Kitam. (Asteraceae)	Aqueous extract	*In-vitro*: Compound 48/80 induced RPMC.	0.001–1 mg/ml	Dose dependently attenuate histamine release and reduce intracellular calcium from activated mast cells. Also inhibit the production of IL-6 and other cytokine mediators associated with PCA.	[34]
		In-vivo: Compound 48/80 induced systemic reaction.	0.001–1 g/kg Body weight		

		In-vivo: PCA reaction.	0.01-1 g/kg body weight		
Bauhinia variegata L. (Caesalpiniaceae)	Ethanolic extract	*In-vivo*: Compound 48/80 induced mortality in mice.	400 mg/kg	Reduce mast cell degranulation by 71%and mortality by 50%.	[35]
Baliospermum montanum Blume. (Euphorbiaceae)	Chloroform extract	*In-vivo*: Mice treated with compound 48/80.	200 and 400 mg/kg	Dose dependent inhibition of mast cell degranulation.	[36]
Cassia occidentalis L. (Fabaceae)	Ethanolic extract	*In-vivo*: Egg albumin sensitized rat mast cells.	250 mg/kg	Significant inhibition of mast cell degranulation. But higher doses are cytotoxic.	[37]
Cassia alata L. (Fabaceae)	Hydro methanolic extract	*In-vivo*: Triple Ag or sheep serum induced mast cell degranulation in rats.	200 mg/kg	Significant mast cell stabilizing property. Rhein and Kaempferol showed this effect at 5mg/kg.	[38]
Chrysanthemi sibrici L. (Asteraceae)	Ethanolic extract	*In-vitro*: Dinitro phenol -BSA or compound 48/80-induced degranulation in RBL-2H3 mast cells.	-	Dose dependent inhibition with IC50 values of approximately 49 µg/ml and 76 µg/ml, respectively.	[39]
		In-vivo: Compound 48/80 induced systemic anaphylaxis reaction in mice.	300mg /kg	Dose dependent inhibition up to 48%.	
Cichorium intybus L. (Asteraceae)	Aqueous extract	*In-vitro*: Compound 48/80 induced RPMC.	1-1000 µg/ml	Dose dependent inhibition of histamine release.	[40]
		In-vivo: PCA induced by anti-DNP IgE and systemic anaphylaxis induced by compound 48/80.	1000 mg/kg	Significant inhibitory effect on induced in vivo allergic reactions.	
Cissus sicyoides L (Vitaceae)	Methanolic extract	*In-vitro*: Compound 48/80 induced histamine release from RPMC.	0.5 mg/ml	Significant inhibition of histamine release.	[41]
Clerodendrum serratum (L.) Moon. (Lamiaceae)	Aqueous extract	*In-vivo*: Clonidine induced mast cell degranulation in rats.	100 mg/kg, i.p.	73% inhibition of degranulation of mast cells.	[42]

Clinopodium gracile (Benth.) Kuntze (Lamiaceae)	Water extract	*In-vivo*: Compound 48/80-induced systemic anaphylaxis and immunoglobulin E-mediated cutaneous anaphylaxis.	1–100 mg/kg Body weight, i.p.	Inhibition of anaphylactic reactions and histamine release dose dependently by modulating intracellular calcium.	[43]
		In-vitro: Phorbol 12-myristate 13-acetate and calcium ionophore A23187-stimulated human mast cells.	1–100 µg/ml	Attenuation of gene expression and release of pro inflammatory cytokines mediated by NF- KB.	
Cressa cretica L. (Convolvulaceae)	Ethyl acetate and methanolic fraction	*In-vitro*: Acetylcholine and histamine aerosol-induced broncospasm using guinea pigs and egg albumin and compound 48/80 on isolated rat peritoneal mast cells.	-	Ethyl acetate fraction showed more significant bronchodilatory and mast cell stabilizing activity	[44]
Curculigo orchiodes Gaertn. (Amaryllidaceae)	Alcoholic extract	*In-vivo*: Compound 48/80 induced degranulation of rat peritoneal mast cells.	100-400 mg/kg	Increase in total number of intact mast cells indicates its mast cell stabilizing potential.	[45]
Dracocephalum argunense Fisch. ex Link (Labiatae)	Aqueous extract	*In-vivo*: Compound 48/80 induced systemic reaction in mice.	0.001—1 mg/g, anally	Reduced release of histamine and pro inflammatory mediators from activated mast cells.	[46]
Elaeocarpus sphaericus (Gaertn.) K. Schum. Elaeocarpaceae	Petroleum ether, benzene, chloroform, acetone and ethanol extracts	*In-vitro*: Rat mesentric mast cell model	-	Mast-cell stabilizing activity	[47]
Eriobotrya japonica (Thunb.) Lindl. (Rosaceae)	-	*In-vitro*: Compound 48/80-induced systemic anaphylactic reactions and serum histamine release in mice and IgE-mediated passive cutaneous anaphylaxis.	-	Dose dependent inhibition of histamine release and systemic anaphylactic as well as PCA reaction.	[48]

Fagopyrum esculentum Moench (Polygonaceae)	Grain extract	*In-vitro*: Compound 48/80-induced vascular permeability and RPMC degranulation.	-	Potential anti allergic due to inhibition of histamine release and cytokine mediators.	[49]
		In-vivo: Anti - dinitrophenyl IgE activated PCA reaction.			
Forsythia koreana (Nakai) T.B.Lee. (Oleaceae)	Methanolic extract	*In-vitro*: Compound 48/80 induced RPMC degranulation.	1 mg/ml	Inhibition of histamine release from the RPMCs by 13.8% and TNF-alpha, IL-6, and IL-8 production from HMC-1 cells by 71.16%, 86.72% and 44.6%, respectively.	[50]
		In-vivo: Compound 48/80-induced systemic anaphylaxis and anti-dinitrophenyl IgE-induced PCA	1 g/kg	Only 50% induced mortality was seen.	
Ficus bengalensis L. (Moraceae)	Aqueous, ethyl acetate extract and methanol Extract	*In-vivo*: Clonidine induced mast cell degranulation.	100 mg/ kg i.p.	Inhibition of mast cell degranulation was variable ranging from 65-75% depending on type of extract.	[51]
Ficus religiosa L. (Moraceae)	Aqueous extract	*In-vivo*: Histamine and acetylcholine induced bronchospasm in guinea pigs and mast cell stabilizing activity	150 and 300 mg/kg	Relieve bronchospasm and mast cell stabilizing activity	[52]
Glyphaea brevis Monachino (Tiliaceae)	70%v/v aqueous ethanol stem bark extract	*In-vivo*: Systemic anaphylaxis induced by compound 48/80.	30, 100, and 300 mg/kg	Inhibits the in vivo degranulation of mast cells and thereby suppress allergy dose dependently and delaying the induced mortalities the time for compound 48/80-induced mortality.	[53]
Isodon japonicus (Burm.f.) H.Hara (Labiatae)	Aqueous extract	*In-vivo*: Compound 48/80 induced histamine release from RPMC and systemic anaphylaxis.	-	Dose dependent inhibition of histamine release and induced systemic reaction.	[54]
Lycopus lucidus Turcz. ex Benth. (Lamiaceae)	Aqueous extract	*In-vivo*: Compound 48/80 induced degranulation of RPMC, systemic anaphylaxis reactions and	0.005-0.1 g/kg	Dose dependent reduction in histamine release, inhibition of systemic anaphylaxis and PCA reaction.	[55]

		PCA.			
Magnolia obovata Thunb. (Magnoliaceae)	Methanolic extract	*In-vitro*: Compound 48/80 induced histamine release.	-	Dose dependently inhibits histamine release.	[56]
Magnolia officinalis Rehder & Wilson (Magnoliaceae)	Aqueous extract	In vitro: RPMC activated by compound 48/80 or anti-dinitrophenyl or IgE.	0.001 to 1 mg/ml	Inhibit histamine release and TNF-α production dose dependently.	[57]
		In vivo: Compound 48/80 induced systemic anaphylactic reaction in rats and IgE mediated PCA reaction.	0.01 to 1 g/kg	Dose dependently inhibits histamine release, PCA and systemic anaphylaxis.	
Mallotus philippinensis (Lam.) Muell. Arg. (Euphorbiaceae)	Rottlerin	*In-vivo*: Passive cutaneous and passive systemic anaphylaxis mouse models, and anaphylactic contraction of bronchial rings isolated from sensitized guinea pigs.	-	Prevention of IgE-mediated cutaneous vascular extravasation, hypothermia, elevation in plasma histamine level and tracheal tissue mast cell degranulation in mice in a dose-dependent manner. Suppression of ovalbumin-induced guinea pig bronchial smooth muscle contraction and IgE-mediated immediate release of β-hexosaminidase from RBL-2H3 mast cells.	[58]
Ocimum sanctum L. (Lamiaceae)	Ethanolic extract	*In-vivo*: Albino rats sensitized by horse serum along with triple antigen containing Bordetella pertusis.	100 and 200 mg/kg body weight	Dose dependent inhibition of mast cell degranulation to an extent of 62.44 -67.24%.	[59]
	Flavonoid fraction		75 and 150 mg/kg body weight	Dose dependent inhibition of mast cell degranulation to an extent of 54.62 and 60.48% respectively.	
Perilla frutescens (L.) Britton (Lamiaceae)	Aqueous extract	*In-vitro*: RPMC activated by compound 48/80 or anti-DNP IgE.	10-3 to 1 mg/ml	Inhibits mast cell-mediated immediate-type allergic reactions *in-vivo* and *in-vitro* dose dependently.	[60]
		In-vivo: Systemic allergic reaction induced by compound 48/80 and local allergic reactions activated	0.05 to 1 g/kg		

		by anti-DNP IgE in rats.			
Phyllanthus emblica L. (Phyllanthaceae)	Methanolic extract	*In-vitro*: Compound 48/80-induced mast cell degranulation.	2, 4 and 6 mg/ml	Showed potent dose dependent inhibition of mast cell degranulation.	[61]
Pithecellobium clypearia Benth (Fabaceae)	Polyphenol-rich ethanol extract	*In-vitro*: Compound 48/80 induced histamine from rat peritoneal mast cells		Significant inhibition effect on histamine release.	[62]
	Seven main polyphenols (including (-)-epigallocatechin-7-gallate), (-)-5, 7, 3', 4', 5'-pentahydroxyflavan), and (-)-tetra hydroxyflavan-7-gallate)	*In-vivo*: Croton oil-induced ear edema, carrageenan-induced paw edema and DNFB-induced delayed hypersensitivity reaction		Anti-inflammatory and anti-allergic activities	
	Ethanol extract	*In-vitro*: Compound 48/80 induced histamine from rat peritoneal mast cells		Concentration-dependent reduction in histamine release from rat peritoneal mast cells and increased intracellular cAMP content of rat mast cells	
Plumbago zeylanica L. (Plumbaginaceae)	Ethanol extract; Hydro alcoholic 70% v/v	*In-vitro*: Compound 48/80 induced activation of rat mesenteric cells.	10 and 100 µg/ml	Inhibit mast cell derived immediate type allergic mast cell degranulation.	[63]
		In-vivo: Systemic anaphylactic shock induced by compound 48/80 in mice	500, 1000 mg/kg, p.o.	Inhibits mast cell-dependent immediate allergic reactions	
Pothos scandens L. (Araceae)	Aqueous extract	*In-vitro*: Compound 48/80–induced histamine release RPMC	1, 10, 100 µg/ml	Dose dependently inhibits histamine release	[64]
Prunella vulgaris L.(Labiatae)	Aqueous extract	*In-vivo*: Compound 48/80-induced systemic anaphylaxis and serum histamine release in mice	0.001-0.1 g/kg	Mast cell stabilizing and antiinflammatory	[65]
Punica granatum L. (Lythraceae)	Extract and its ellagic acid rich fraction	*In-vivo*: Dextran sulfate sodium induced ulcerative colitis in mice	100 and 200 mg/kg p.o.	Attenuated the dextran sulfate sodium induced rise in colonic histamine level	[66]

Randia dumetorum (Retz.) Poir. (Rubiaceae)	Ethyl acetate and methanol extracts	*In-vivo*: Acetylcholine and histamine induced contraction and Compound 48/80 induced mast cell degradation	100 mg/kg	Inhibited contractions and experimentally induced inflammation. Antioxidant and decrease in histamine release.	[67]
Rehmannia glutinosa (Gaertn.) Steud. (Phrymaceae)	-	*In-vivo*: Compound 48/80 induced systemic anaphylactic shock.	0.0001 -1 g/kg	Exhibited significant dose dependent mast cell stabilizing potential.	[68]
Rosa davurica Pall. (Rosaceae)	-	*In-vitro*: Compound 48/80 and IgE-mediated histamine release from RPMC	0.0001 to 1 g/kg	Inhibited histamine release at concentrations from 0.001 to 1 µg/ml	[69]
		In-vivo: Compound 48/80 activated systemic anaphylaxis in mice.		Dose dependently reduced mortality	
Rhus javanica L. (Anacardiaceae)	Aqueous extract	*In-vitro*: Compound 48/80-induced or IgE-medated histamine release from RPMC	0.001–0.1 mg/ml	Dose-dependently inhibited compound 48/80-induced or IgE-mediated histamine release from RPMC.	[70]
		In-vivo: Compound 48/80-induced systemic allergic reaction	1 to 100 mg/kg, i.p.	Significant anti allergic action possibly due to inhibition of histamine release.	
Rubus suavissimus S. Lee (Rosaceae)	Aqueous extract	*In-vitro*: Compound 48/80 activated RPMC.	0.001 to 1 mg/ml	Dose dependent inhibition of histamine release from peritoneal mast cells and systemic anaphylaxis indicates its potential to treat immediate-type allergic reaction.	[71]
Sanguisorba officinalis L. (Rosaceae)	Aqueous extract	*In-vitro*: Compound 48/80 or anti-DNP IgE-induced induced RPMC activation.	0.001 to 1 mg/mL	Significant inhibition of histamine in both *in-vitro* model	[72]
		In-vivo: Systemic allergic reaction induced by compound 48/80 in mice	0.01 to 1 g/kg	Pretreatment with extract reduced mortality in mice dose dependently	

Schinus terebinthifolius Raddi (Anacardiaceae)	Aqueous extract, ethyl acetate fraction, gallic acid, methyl gallate, 1,2,3,4,6-pentagalloyl glucose	*In-vitro*: RPMC activation by compound 48/80 and IgE	50-500 µg/ml extract and its fraction; 100 µg/ml compounds from fraction	Pretreatment with the fraction and compounds reduced histamine release significantly	[73]
Schizonepeta tenuifolia Briq (Lamiaceae)	Aqueous extract	*In-vitro*: Compound 48/80 and IgE - mediated histamine release from RPMC	-	Dose dependently inhibited compound 48/80-induced or IgE-mediated histamine release	[74]
		In-vivo: Compound 48/80 induced systemic anaphylaxis in rats	0.005 to 1 g/kg	100% reduction in mortality was achieved with all the test doses	
Scrophularia buergeriana Miq.(Scrophulariaceae)	70% Ethanolic extract	*In-vitro*: RBL - 2H3 mast cells.	-	Inhibited the release of β-hexosaminidase and histamine along with suppression of cytokine expression particularly that of TNF -α and interleukin-4.	[75]
Selaginella tamariscina (P.Beauv.) Spring (Selaginellaceae)	70% Ethanolic extract	*In-vitro*: Histamine release induced by compound 48/80 or ovalbumin from RPMC	50, 100 and 200 µg/ml	Significant inhibition of histamine in both *in-vitro* tests. The extract (200 µg/ml) also normalize the cAMP levels in RPMC	[76]
		In-vivo: Systemic anaphylactic shock induced by compound 48/80 in mice	500 and 1000 mg/kg	Pretreatments with extract reduced dose-dependently mortality rate upto 40%	
Solanum nigrum L. (Solanaceae)	Petroleum ether, ethanol and aqueous extracts	*In-vitro*: Clonidine induced mast cell degranulation in isolated peritoneal fluid from mice	50,100 and 200 mg/kg, i.p.	Petroleum ether extract show maximum protection against mast cell degranulation dose dependently as compared to other extracts.	[77]
Sphaeranthus indicus L. (Asteraceae)	Different extracts	*In-vivo*: Compound 48/80 and sheep serum induced mast cell degranulation model	100, 150 and 300 mg/kg	Ethanol and ethyl acetate extracts show potent mast cell stabilizing effects	[78]
Stachys riederi (Ledeb.) H. Hara (Labiatae)	Aqueous extract	*In-vivo*: PCA activated by anti-DNP IgE; Compound 48/80 or anti-	-	Significant inhibition of rat peritoneal mast cell degranulation and anaphylaxis reaction	[79]

		DNP IgE-induced induced RPMC activation.			
Syzygium cumini (L.) Skeels (Myrtaceae)	Aqueous extract	*In-vitro*: Compound 48/80 induced histamine release from RPMC	1 µg/ml	Show 49.5% inhibition of histamine release	[80]
Teucrium japonicum Houtt. (Lamiaceae.)	Aqueous extract	*In-vitro*: Compound 48/80 induced histamine release from RPMC	0.001 to 1 mg/ml	Inhibit histamine release thus inhibiting mast cell mediated allergic reactions by modulating intracellular calcium, TNF-alpha, and NF-KB.	[81]
		In-vivo: Compound 48/80-induced systemic anaphylaxis; IgE mediated PCA reaction	1000 mg/kg		
Tinospora cordifolia Willd. (Menispermaceae)	Aqueous extract	*In-vitro*: Compound 48/80 and anti-DNP IgE induced histamine release from RPMC.	0.01 to 10 mg/ml	Concentration dependent inhibition of histamine release and induced mortality indicating its efficacy in various acute and chronic allergic disorders.	[82]
		In-vivo: Compound 48/80 induced systemic reaction in mice			
Vigna angularis (Willd.) Ohwi & Ohashi (Fabaceae)	95 % ethanol extract	*In-vitro*: Phorbol 12-myristate 13-acetate and calcium ionophore A23187 induced histamine release from human mast cell line (HMC-1 cells)	-	Dose dependently inhibits histamine release and systemic anaphylaxis	[83]
		In-vivo: Compound 48/80 induced systemic anaphylaxis in mice	10, 50 and 250 mg/kg		
Vitis amurensis Rupr (Vitaceae)	70% methanol extract	*In-vitro*: Compound 48/80 induced and IgE-mediated histamine release form RPMC	0.001–1 mg/ml	Dose dependent reduction in mice mortality upto 80%	[84]

		In-vivo: Compound 48/80–induced systemic reaction in mice	1 - 1000 mg/kg		
Vitex negundo L. (Verbenaceae)	Ethylacetate extract and its various fraction	*In-vivo*: PCA induced in rat.	200 mg/kg	Potent anti-allergic effect as indicated by reduced leakage of dye. Active compound was found to be 5-hydroxy-3, 6, 7, 3', 4'-pentamethoxy flavone.	[85]
Xanthium strumarium L. (Asteraceae)	Aqueous extract	*In-vitro*: Compound 48/80 induced degranulation of mesenteric mast cells.	0.01–1 mg/ml	Dose dependent inhibition of histamine release	[86]
		In-vivo: Compound 48/80-induced systemic anaphylaxis	10 to 1000 mg/kg	Mortality was reduced upto 0% in dose dependent manner	
Zizypus mauritiana Lam. (Rhamnaceae)	95% ethanol extract	*In-vivo*: PCA and compound 48/80 induced mast cell degranulation in rats	250, 500 and 1000 mg/kg	Pretreatment with extract reduced dose dependently passive cutaneous reaction and histamine release in rat peritoneal fluid	[87]

HMC- Human mast cells; LD50- Lethal dose; RPMC- Rat peritoneal mast cells; PCA- passive cutaneous anaphylaxis; IgE- Immunoglobulin E; IC50¬- Inhibitory concentration at which 50% inhibition occur; IL- interleukin; DNP- Dinitro phenol; TNF-α – Tumour necrosis factor; cAMP- cyclic adenosine monopohosphate

RESULTS AND DISCUSSION

Plant polyphenols are reported to have anti-inflammatory activity and inhibitory effect against histamine release [8,9]. Plants containing flavonoids have been reported to possess antihistaminic and antiallergic effect [10, 11]. Quercetin, a ubiquitous flavonoid, has been reported to inhibit phospholipase A (responsible for liberating arachidonic acid from membrane phospholipids), lipoxygenase (responsible for converting arachidonic acid into leukotrienes) [12], platelet aggregation, and mast cell and basophil degranulation [13,14]. Quercetin has also been shown to bind to calcium/calmodulin complexes thus preventing the influx of calcium into mast cells and basophils necessary for degranulation of mast cells [15]. Moreover polyphenols have significant antioxidant effect that counters the production of oxygen free radicals which are reported to be involved in the pathogenesis of numerous disorders including mast cell degranulation [16,17].

In the past two decades numerous plants have been investigated for management of allergic/ immune disorders involving mast cells degranulation (Table-1). *In-vitro* and *in-vivo* models have been developed to determine the mast cell functions [18]. *In-vitro* tests involve use of cell lines and isolated mast cells. Mast cells are isolated from bone marrow or from rodent peritoneal cavities; these are called bone marrow mast cells (BMMC) or peritoneal cavity mast cells (PCMC) respectively. PCMC are preferred since these retain their morphology and function and release histamine when exposed to mast cell activators [19]. Mast cells may also be isolated from embryonic stem cells [20]. These isolated cells are exposed to mast cell activators/ degranulators like Compound 48/80, specific allergens, IgE, NSAIDS, iodine containing dyes etc. Compound 48/80 (a polymer formed by condensation of N-methyl-p-methoxyphenethylamine with formaldehyde) is frequently employed in *in-vitro* models as it is causes significant release of histamine from mast cells. The prevention of histamine release from the mast cells is an index of mast cell stabilization [21]. *In vivo* models involve antigen-induced (for example use of egg albumen, horse serum etc) challenge of mast cells. Subsequently hematological parameters are evaluated or after sacrificing animals the mesentery is

collected, stained with 0.1% toluidine blue observed microscopically to calculate percent intact and disrupted mast cells [22]. KIT-mutant mice have also been developed to further explore the functions of mast cells [23].

In conclusion, mast cell stabilization is a complex phenomenon. Polyphenols with their multi-target functioning may thus be suitable candidates for prevention of mast cell degranulation. The large number of plants described in this review clearly demonstrated the importance of plants rich in polyphenols in the mast cell stabilization, although the mechanism of action is not clearly elucidated for many plants / plant extracts showing mast cell stabilizing activity. Thus the need of the hour is methodical evaluation of the plants that have shown mast cell stabilizing potential with a precise goal of developing plant polyphenols as effective and safe mast cell stabilizers.

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