

The Inhibitory Effects of Tetracycline on Mastocytosis

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Abstract

Mastocytosis is a rare disease that causes its victims pains in the body, anaphylactic shocks and in some cases death. There is currently no cure for this disease but there are some medications taken to manage the symptoms of this disease. The cause of mastocytosis is the overabundance of mast cells in the blood stream, body tissues, and bone marrow. These mast cells are well meaning hematopoietic cells which are members of the body's response to an allergy. It has been established that tetracyclines possess anti-bacterial properties, but recent development has also shown that it also possesses anti-inflammatory properties as well as apoptotic properties which can be applied in the treatment of mastocytosis. This paper focuses on the use of the principle of "Creative synthesis" to formulate a possible treatment to mastocytosis using tetracycline and polyphenols as well as chemically modified tetracyclines (CMTs). In addition, investigations will be carried out to proffer a possible combination which will help in inhibiting the effects of mastocytosis. Based on the synthesis, an economic analysis will be carried out to show the economic potential of this proffered treatment.

Keywords

Tetracycline, Chemically Modified Tetracycline, Mast Cells, Mastocytosis, Polyphenols

1. Introduction

As much as the cells perform a well-meaning agenda within the body by responding to foreign allergens, it is also reported to function in manners that lead from an annoying to catastrophic reactions and possibly contribute to the pathology of autoimmune diseases [1].

The term mast cell activation disease represents a stack of disorders described

by:

- 1) The pathological mast cell accumulation in conceivably any or all organs and tissues as well as;
- 2) Atypical release of variable subsets of mast cell mediator [2].

The mast cell activation disease encompasses diseases described by the buildup of genetically modified mast cells and additionally unusual release of these cell mediators, influencing functions in possibly every organ system, regularly without causing variations from the norm in routine laboratory or radiologic testing. In most of the cases associated with mast cell activation disease, the diagnosis is achieved through relatively non-invasive examination. Viable treatment regularly comprises just of antihistamines and mast cell membrane-stabilizing compounds supplemented with medications focused at particular side effects and complications [2].

In most patients, the cause of the disease is from the activating mutation (D816V) in the gene coding for the stem cell factor receptor c-kit, which is present on mast cells. The resulting effect is the auto phosphorylation of the receptor, which is responsible for uncontrolled mast cell proliferation. Mast cell activation disease is currently recognized to likely be significantly pervasive and along these lines ought to be considered routinely in the differential diagnosis of patients with incessant multisystem polymorbidity or patients in whom an absolutely diagnosed major ailment does not well account for the totality of the patient's presentation. This research looks into creative ways of inhibiting the uncontrolled release of bioactive mediators into the body responsible for causing mastocytosis with the polyphenol tetracycline. This method used is creative synthesis and associative thinking. I am taking an out of the box thinking about mast cells and the possibility of using tetracycline for the treatment of mastocytosis.

1.1. Technical Background

The process of hematopoiesis has to do with the differentiation of multipotent cells into blood and immune cells. These multipotent hematopoietic stem cells give rise to many different cell types which include the cells of the immune system and that of the red blood cells, as seen in **Figure 1** [3] [4].

Mast cells are immune cells of hematopoietic source found in every single human tissue, particularly at the environmental interfaces. They go about as both effector and coordinator cells and assume a focal part in modifying and intrinsic immunity [6] [7]. Their critical part in immunological and also non-immunological procedures is reflected by the extensive number of mediators (>200) including pre-stored ones, for example, histamine and tryptase and in addition numerous mediators that are resynthesized as a response to the non-immune or allergic triggers, for example, chemokines and cytokines, through which the mast cells may impact other different cells [8]. Their developed multitudes of sensory and response systems induce different chaos when mast cells defect develops.

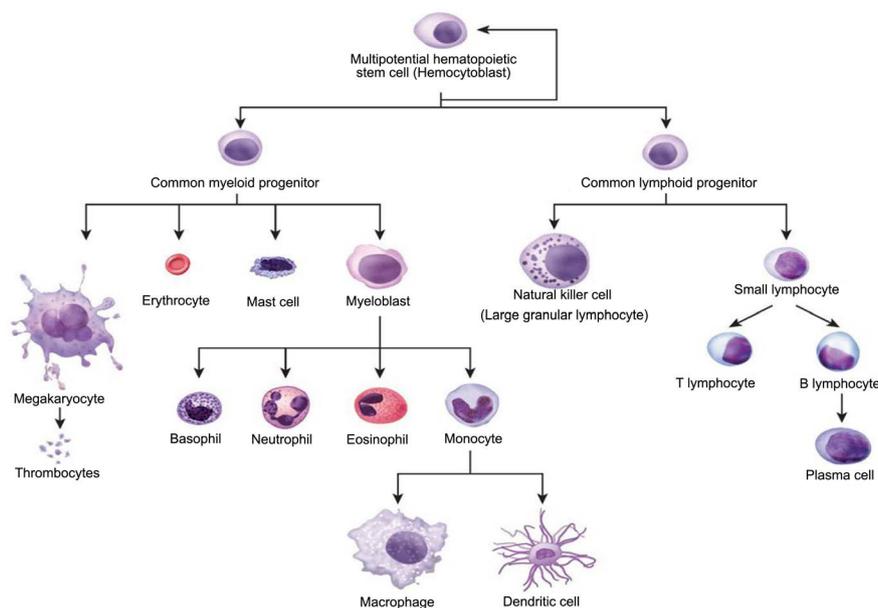


Figure 1. Image of hematopoietic stem cell breakdown [5].

The mast cell is a one of a kind effector part of the immune system described by the existence of metachromatically staining secretory granules, surface expression of the high affinity of IgE receptor (FcεRI), and localization at tissue sites which are adjacent to the microvasculature and at mucosal and epithelial surfaces [9]. The basophils, eosinophils, neutrophils, platelets, macrophages, and certain subsets of lymphocytes additionally contain secretory granules (Figure 2); yet of these granulated cells just the mast cell and basophil express FcεRI. FcεRI expression was once thought-out as exclusively for mast cells and basophils, yet two groups have now given solid confirmation that the epidermal langerhans' cell transcribes and expresses the entire tetrameric FcεRI molecule on the surface [10]. It has also been discussed that the FcεRI presence on mast cells and basophils empowers these two cells to be actuated by the adhering of the IgE to FcεRI and resulting cross-linking when a particular antigen is encountered.

The acknowledgment that mast cells discharge an extensive variety of proinflammatory, immunomodulatory, and mitogenic cytokines, mediators that are lipid-derived, and nonpartisan proteases and also the exhibition of functional surface IgG receptors on these cells propose that mast cells most likely assume a more central part in immune and inflammatory processes than those customarily considered. The creation of immunomodulatory cytokines, for example, interleukin-4 (IL-4), by mast cells which can prompt T-helper cell differentiation, is one case of how mast cells may work as regulators and additionally effector components of the immune response as observed in Figure 3.

Figure 4 shows the response mechanism of mast cells. Despite the fact that mast cells differ from the pluripotential hematopoietic immature microorganism, the conferred precursors are not yet distinguishable in the blood. The progenitor forms transverse the vascular space to gain passage to tissue sites where

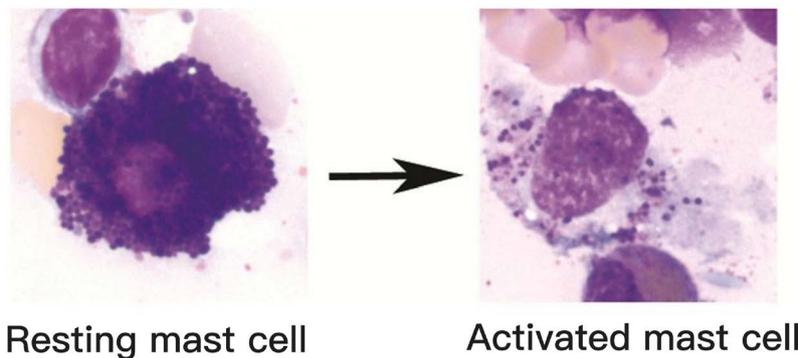


Figure 2. May-Grünwald/Giemsa stain of a resting human mast cell and a mast cell following activation-induced degranulation. Note the loss of granule staining. Mast cells obtained from the human bone marrow, magnification 1000× [2].

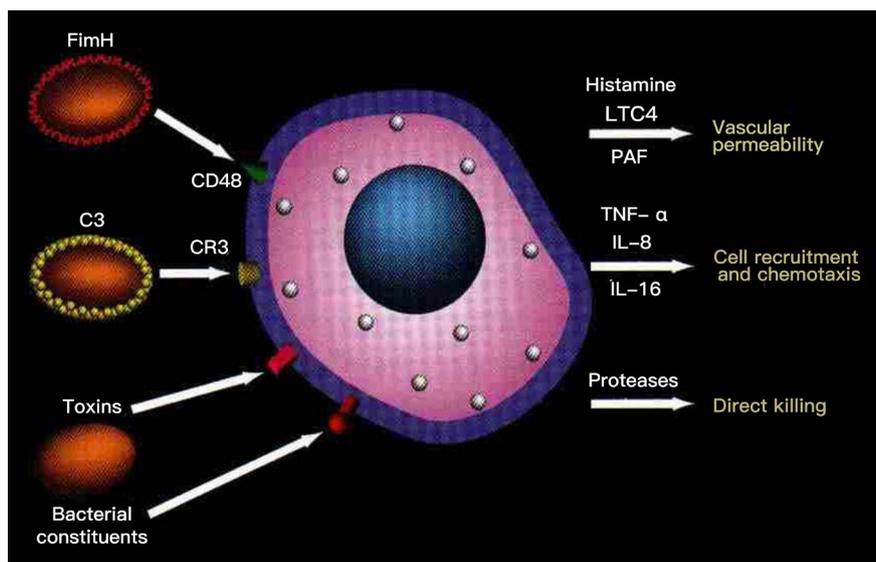


Figure 3. Mast cell-microorganism interactions. Microorganisms such as bacteria or parasites or their products interact with mast cells through specific receptors. This interaction results in mast cell activation and mediator release which elicit an inflammatory response or direct killing leading to bacterial clearance [11].

there will be more proliferation, differentiation, and maturation can happen in light of tissue and organ specific factors [9]. Conversely, basophils develop completely in the bone marrow and are terminally differentiated, the short-lived members from the blood granulocyte compartment where they react to inflammatory mediators by endothelial cell adhesion, extravascular migration, chemotaxis, and activation at the sites of particular inflammation [9].

1.2. Mast Cell Activation/Secretion Coupling

At the point when mast cells are exposed to particular multivalent antigen or immune complexes, cross-connecting of Fc ϵ RI or Fc γ RIII brings about a unified noncytolytic series of events termed “activation”. Activation by Fc ϵ RI cross linking brings about the cell degranulation or “exocytosis” indicated by a discharge of

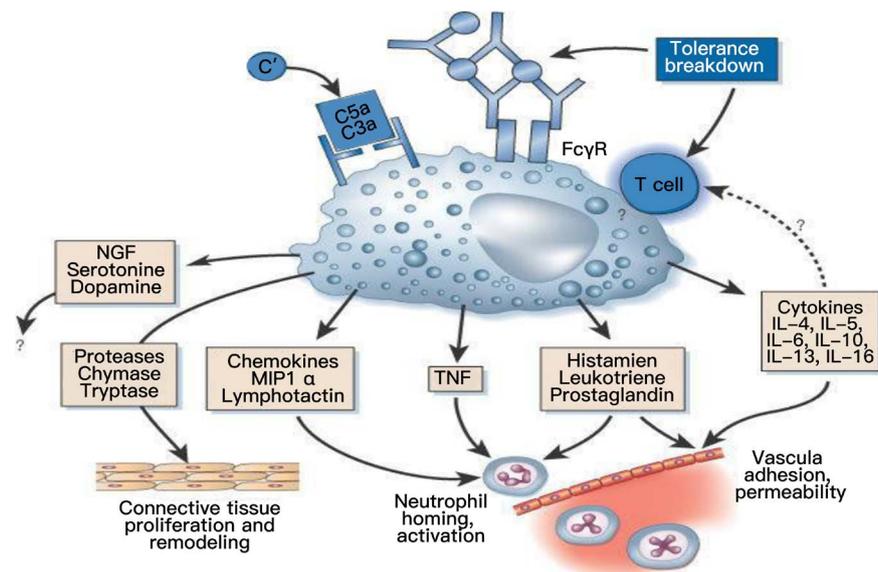


Figure 4. Mast cells are known to be the essential responders in allergic reactions, coordinating responses to small measures of allergens. A lot of recent observations demonstrate that they may likewise have a key part in organizing the early phases of immune system illnesses, especially those including auto-antibodies [12].

bioactive mediators from secretory granules, the biosynthesis and discharge of recently formed mediators gotten from arachidonic acid, and a wide panel of cytokines that are synthesized or secreted, as seen in **Figure 5** [9].

The monomeric IgE binding to FcεRI as such is thought not to bother the receptor or to bring about cellular events. The gathering of FcεRI by resulting binding of multivalent antigen triggers mast cell activation. The earliest perceived event is phosphorylation of particular substrates, including autophosphorylation of the β and γ subunits and phospholipase Cγ (PLCγ) [14] [15] by means of tyrosine kinase activity, which copurifies with IgE receptor complexes. Three kinases p56lyn, pp60c-src, and p62c-yes are activated after FcεRI is cross-linked [16]. In addition, it appears that in any event some of these tyrosine kinases closely correlate with FcεRI and are in charge of the initial phosphorylation of PLCγ, potentially through interaction with a conserved motif in the cytoplasmic part of the FcεRI-B and FcεRI-γ chains [17]. The activation of PLCγ constitutes one early transduction pathway; a second pathway includes tyrosine phosphorylation of a 72-kd substrate known as pp72. The resulting events in the pp72 pathway are obscure [18]. The development in intracellular calcium starts activation of calmodulin-dependent pathways, including the phosphatase calcineurin. Calcineurin possibly controls the activity of various transcription factors that are imperative to cytokine gene expression in T lymphocytes [19] and mast cells [20]. It is possible that additional mechanisms are responsible for altering the quantity of DNA-binding proteins that manage transcription of extra genes including those that encode cytokines. The various bioactive molecules provided by the mast cells are simply considered as results of three compartments: preformed

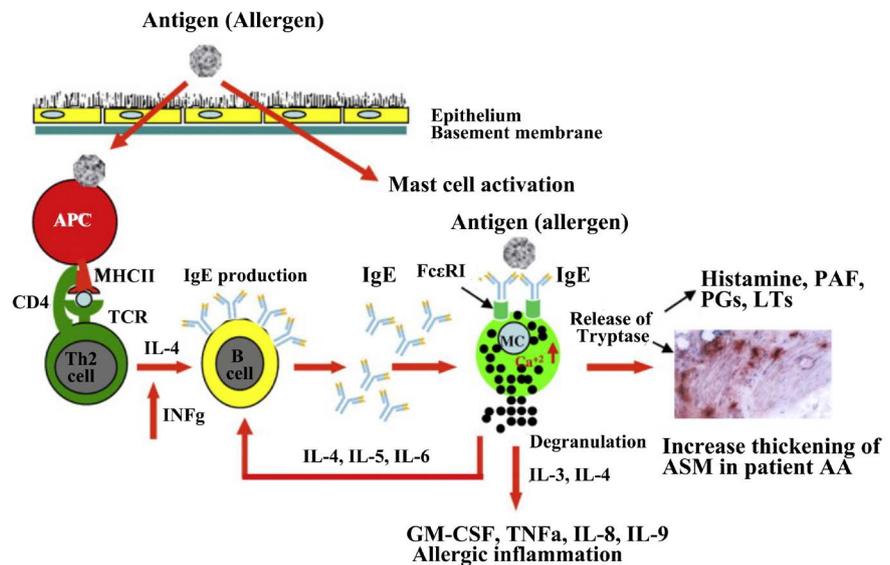


Figure 5. Mast cells in development of allergy [13].

secretory granule middle people and deciphered and deciphered mast cell cytokines. **Table 1** shows different mast cell mediators.

1.3. Roles of Mast Cells in Acute Inflammation

Various research in mast cell-deficient and reconstituted mice have exhibited that mast cells in particular, though restricted, models of inflammation enhances many characteristics of immunologically non-specific acute inflammatory responses [11]. These reactions are indicated by an influx of leukocytes (mostly neutrophils), edema, and changes in the caliber and permeability of the microvasculature. From experimental procedures, mast cells have appeared to be required for the full expression of the tissue swelling and leukocyte infiltration related with the response to the epicutaneous use of PMA or to the intraperitoneal infusion of thioglycollate [21]. Mast cells have likewise been observed to be essential for the induction of a neutrophil influx in immune complex-mediated reactions. This effect has been ascribed to the capacity of mast cells to make and secrete $\text{TNF-}\alpha$, as $\text{TNF-}\alpha$ levels were essentially diminished in the mast cell-lacking W/W^v mice in addition to the reduction in local neutrophil accumulation. Mast cell reconstitution adjusts $\text{TNF-}\alpha$ levels and neutrophil activation [22]. This induction of immune complex-mediated mast cell-dependent inflammation appeared to include IgG Fc receptors. This proposes that mast cells may add to as well as start these responses, as mouse mast cells express $\text{Fc}\gamma\text{RII}$ and $\text{Fc}\gamma\text{RIII}$ [23].

1.4. Mastocytosis

Mastocytosis is a moderately uncommon disease portrayed pathologically by mast cell hyperplasia in the skin and other organ, for example, the gastrointestinal tract, bone marrow, lymph nodes, liver, and spleen. Some of the medical

Table 1. Mast cell mediators [9].

Preformed secretory granule mediators
<ul style="list-style-type: none"> • Histamine • Proteoglycans • Serine proteases • Chymases • Tryptases • Carboxypeptidase A
Lipid-derived mediators (newly formed)
<ul style="list-style-type: none"> • Leukotriene • Leukotriene C4, D4, and E4 (SRS-A) • Prostaglandin D2 • Platelet-activating factor (PAF)
Mast cell-derived cytokines
Proinflammatory Cytokines
<ul style="list-style-type: none"> • TNF-α • IL-1α • IL-1β • IL-6 • MIP family
Mitogenic cytokines and/or growth factors
<ul style="list-style-type: none"> • IL-3 • IL-4 • IL-5 • IL-10 • GM-CSF
Immunodulatory cytokines
<ul style="list-style-type: none"> • IL-1α and IL-1β • IL-4 • IL-10 • IFN-γ

symptoms observed with this condition includes, but not limited to, urtication, abdominal pain, pruritus, nausea, vomiting, headache, flushing, diarrhea, and vascular instability. Urticaria pigmentosa, the most well-known skin sign of mastocytosis (shown in **Figure 6**), was depicted by Nettle-transport in 1869 [24]. Over the top quantities of mast cells were identified in the lesions of urticaria pigmentosa by Unna in 1887 (Unna, 1983). In 1949, Ellis [25] detailed the instance of a child with urticaria pigmentosa with the first posthumous evidence implying that mast cell hyperplasia in skin could be related to systemic disease. From that point forward, there has been an increase in acknowledgment of the clinicopathologic diversity of mastocytosis [26]. These improvements have been accompanied by a quick expansion in learning of the development, differentiation, and biologic expression of mast cells, including the recognition of the inception of mast cells from CD34+ human pluripotent cells [26], the description of the growth factor of mast cell which includes interleukin (IL)-3 [27] as well as the c-kit ligand or stem cell factor (SCF) [28], and the depiction of various pleomorphic and redundant mast cell-derived mediators as shown in **Figure 7** [11].



Figure 6. Urticaria pigmentosa lesions on a child [29].

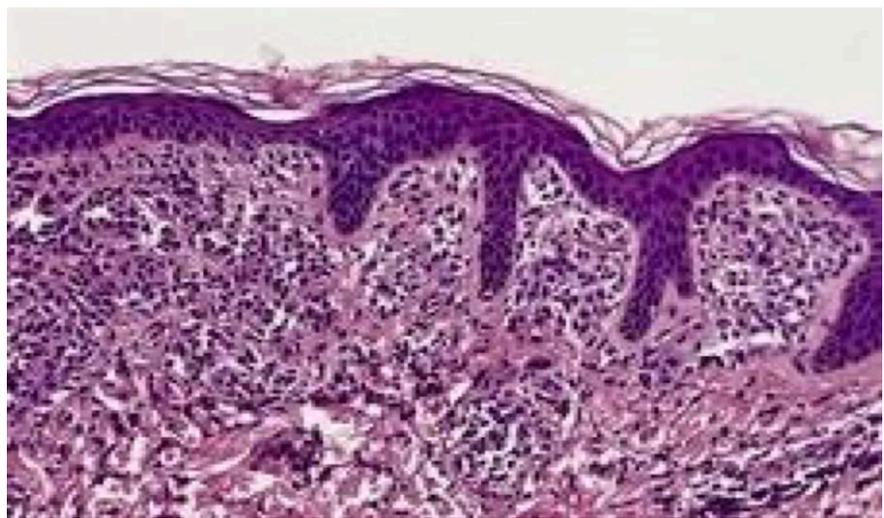


Figure 7. admixture of perivenular lymphocytes and scattered eosinophils [30].

It is unknown the extent to how prevalent mastocytosis currently is, it has been accounted for to be the diagnosed in 1 patient for each 1000 to 2500 new cases found in a dermatology practice or dermatology clinic [31] Mastocytosis can happen at any age and exhibits a slight male-to female predominance. Rare instances of familial mastocytosis have also been reported [32].

Classification

The characterization has been refined by the National Institute of Health by including a group of patients who were named as having lymphadenopathy mastocytosis with eosinophilia [33]. Such patients show, as the term implies, conspicuous rapid advancement of lymphadenopathy, documented mastocytosis, and eosinophilia. Plainly, the mast cell disorders in category II through IV have a more rapid course than the disease as depicted in category I. In classification II the associated hematologic disorder to a great extent decides the course of the disease. Patients with mast cell leukemia have lesser chances of survival in

spite of treatment. Patients with mastocytosis in category IV for the most part live just 2 - 4 years after diagnosis, without chemotherapy.

Other characteristics of mastocytosis are useful in characterizing the categories of patients. For instance, most patients with the indolent variety of the disease have urticaria pigmentosa or diffuse cutaneous mastocytosis sooner or later. However, in categories II through IV, urticaria pigmentosa or diffuse cutaneous mastocytosis is a variable finding. It was additionally seen that patients with mastocytosis that is developing into a leukemic procedure may encounter lost urticaria pigmentosa, should it be present [26]. **Figure 8** shows a concept map of the classification of mastocytosis.

1.5. Tetracycline

In addition to the antibiotic properties of tetracycline, they have also been discovered to exert a number of pleiotropic anti-inflammatory and immunomodulatory activities. These include the capacity to inhibit metalloproteinases (MP), which are an enzyme class involved in important cell functions, for example, the shedding of dissolvable mediators and their receptors from the cell surface, and connection with, the remodeling of the extracellular matrix. It was additionally detailed that doxycycline (DOXY) at therapeutic concentrations (1 - 5 ug/ml) suppresses Ig secretion to a significant extent and class switching by *in vitro* activated murine B cells [35].

Although the complex chemistry of the tetracyclines is beyond the scope of this thesis, in order to appreciate their ability to interact with a wide variety of biomolecules, a simple knowledge of the main features of these compounds is important to. Tetracyclines, such as DOX, and minocycline (MIN), all possess a four-ring core that is attached at various side groups (**Figure 9**). The dimethylamino group, which is located at the C₄ carbon on the upper half of the molecule,

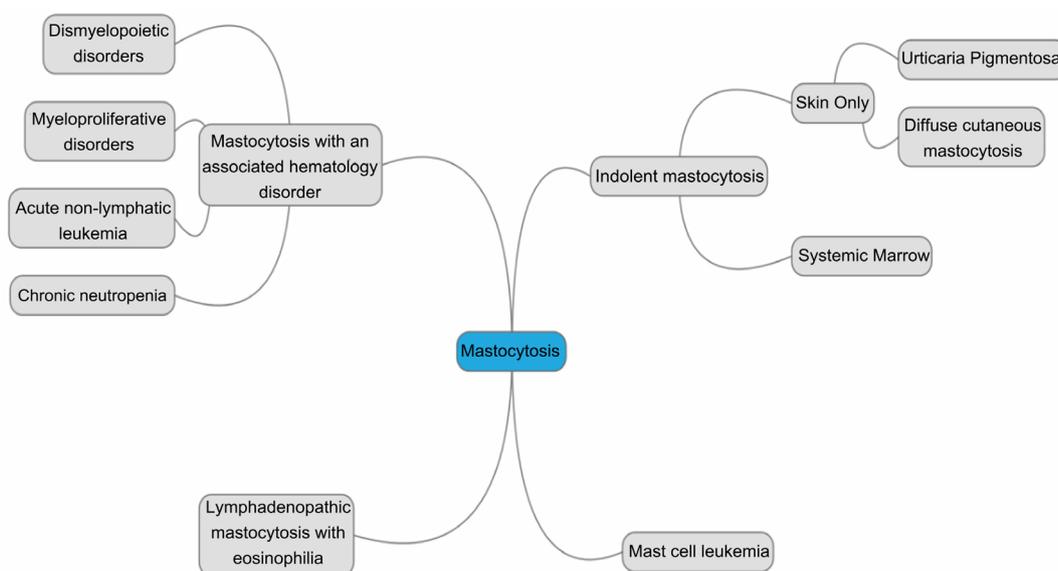


Figure 8. Concept map of Mastocytosis classification [34].

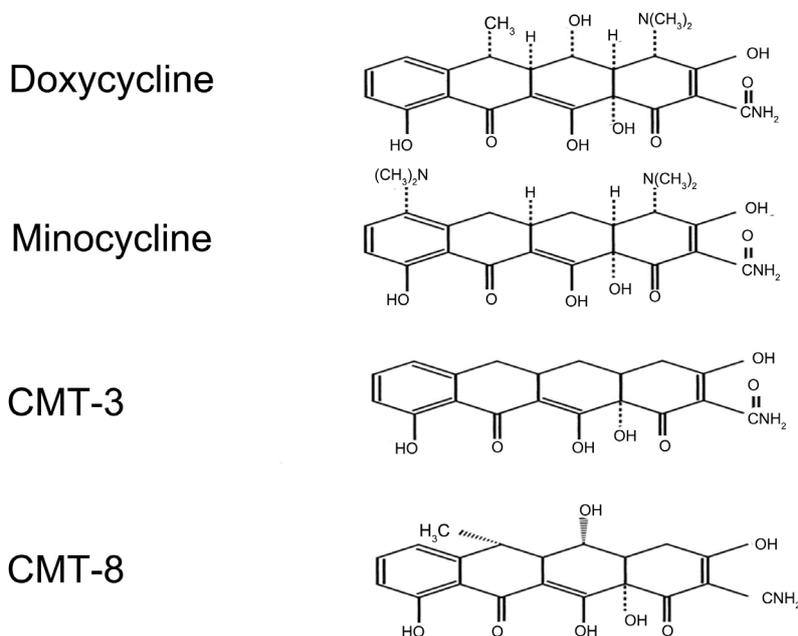


Figure 9. Chemical structure of tetracyclines [36].

has shown to be of major importance to their characteristic antimicrobial activity.

Chemically modified tetracyclines (CMTs) also known as 4-De-dimethylamino tetracyclines lack antimicrobial activities *in vivo* and this may be due to the inability of the molecule to adapt the zwitterionic form that will be necessary for activity [37]. In any case, CMTs do hold the capacity to bind other non-microbial targets, for example, matrix metalloproteinases (MMPs), encouraging their utilization in the treatment of other disease processes [37]. The oxygen-rich lower half of the molecule is very important for binding to both prokaryotic and eukaryotic targets, and obstruction with this area decreases or disposes of the potency of the drug [38]. This region is applicable as a site for the metal ion chelation. The binding of tetracycline to proteins, including the Tet Repressor protein (TetR), might be enormously improved when the tetracycline is complexed with divalent metal ions, for example, Ca^{2+} or Mg^{2+} [39]. The binding of tetracycline to MMPs is believed to be intervened by the chelation of structural and catalytic Zn^{2+} ions inside the enzyme (Figure 10) [38] [40].

Figure 11 above shows the dynamic nature of the tetracycline. The molecule has a modifiable upper region to improve the efficiency of its interaction and a lower non modifiable region. Figure 11 demonstrates the tetracycline's solid skeleton with the possession of the four rings, groups and the upper and lower sides of the molecule in the manner they are usually called. A number of the chemical alterations of both the first and second generation tetracyclines created fluidly active or inactive compounds. A tetracycline which is active (antibacterial activity) must have a linearly arranged DCBA naphthacene ring system with an A-ring C1-C3 di-keto substructure and an exocyclic C2 carbonyl or

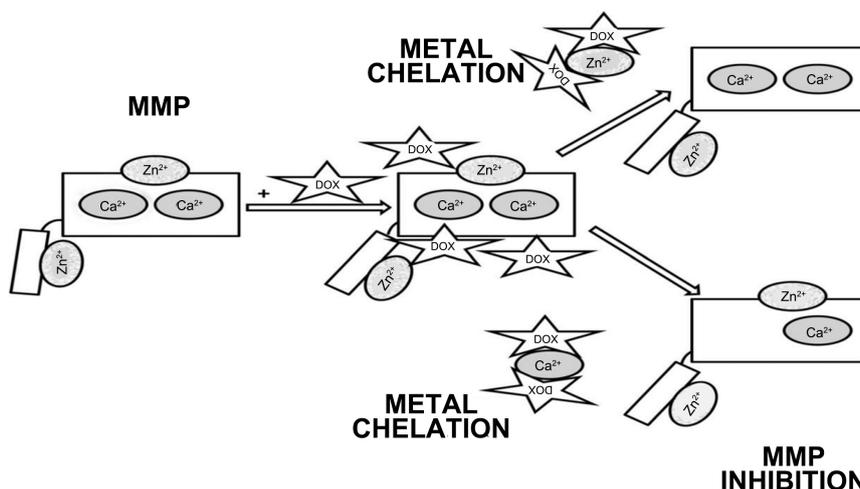


Figure 10. Illustration of means by which doxycycline through zinc and calcium chelation may inhibit matrix metalloproteinases (MMPs) [41].

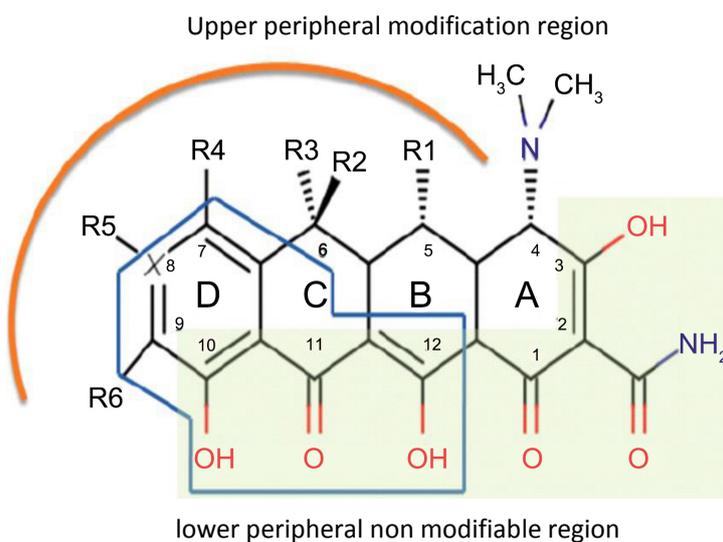


Figure 11. Structure-Activity-Relationship (SAR) of Tetracyclines (TCs). Shaded: Contact region with 30S rRNA. In blue polygonal: same anthracycline region [42].

amide group. All Tetracycline that perform as an inhibitor of protein. Synthesis in bacteria require the amino group in position C4 and keto-enolic tautomers in position C1 and C3 of the A ring [42].

1.6. Matrix Metalloproteinase Inhibition by Tetracyclines

One of the best characterized non-antimicrobial characteristics of the tetracyclines is their ability to inhibit Matrix Metalloproteinase (MMP) family members of endopeptidases. The MMPs are a group of zinc-dependent proteases that are associated with numerous physiological and pathophysiological processes including embryogenesis, tissue remodeling, inflammation, and tumor invasion [43]. MMPs can be subdivided in light of crude substrate specificities into the collagenases, gelatinases, stromelysins, and membrane-type MMPs (MT-MMPs)

[44]. The collagenase groups consist of MMP-1, MMP-8, and MMP-13, and all cleave fibrillar collagens (type I and type III). Collagen parts subsequently denature into gelatins.

The gelatinases incorporate MMP-2 and MMP-9, proteolyze the gelatins. The gelatinases likewise degrade basement collagen (type IV). The stromelysins consists of MMP-3, MMP-7, MMP-10, and MMP-11, and they are fit for debasing proteoglycans, laminin, fibronectin, collagen IV, and others. The cell membrane-anchored MT-MMP consists of six distinctive MMP, of which MT1-MMP is the best described [45]. The suppression of MMPs is gainful in numerous pathological conditions in which MMP-mediated proteolysis of the extracellular matrix (ECM) adds to the pathogenesis, for example, heart remodeling, tumor invasion, and inflammation [43] [46].

1.7. Reactive Oxygen Species

There is an excess production of reactive oxygen species under many pathological conditions, for example, myocardial I-R injury and inflammatory processes which can further lead to the oxidative destruction or the dysfunction of many cellular parts. Reactive oxygen species (ROS) have been said to be highly reactive and consist of free radicals superoxide (O_2^-) and hydroxyl radical (OH), the non-free radicals hydrogen peroxide (H_2O_2), hypochloride (HOCl), and peroxynitrate ($ONOO^-$) [47]. Both DOX and MIN have a multiple-substituted phenol ring similar to vitamin E which is the major key to the ROS-scavenging ability of these compounds. The phenol ring reacts with a free radical to create a more stable and unreactive phenolic radical. It is said that MIN has a more superior scavenging ability and this can be due to the presence of diethylamino group on the phenolic carbon which is exclusive to MIN and it provides the improved steric hindrance [48].

1.8. Proapoptotic Properties of Tetracyclines

In a study completed to observe the cytotoxic impact of Tetracycline Analogs (TCNAs) (Doxycycline, Minocycline and COL-3) in Acute Myeloid Leukemia HL-60 Cells, TCNAs was able to induce a cytotoxic effect in the human leukemia-60 (HL-60) cells in a concentration and time-dependent way. The half maximal inhibitory concentration (IC₅₀) was evaluated after 24 h of incubation with the TCNAs. An IC₅₀ of 1.3 $\mu\text{g/ml}$ was reported, which shows higher sensitivity of the cells to the tetracycline derivative COL-3 than to DOXY and MINO, which was reported to have an IC₅₀ of 9.2 and 9.9 $\mu\text{g/ml}$, respectively These IC₅₀s are in the low scope of sensitivities detailed in cancer cell lines. IC₅₀ in the range of 3 - 10 $\mu\text{g/ml}$ was reported for COL-3, and 10 - 20 $\mu\text{g/ml}$ for DOXY [49] [50]. MINO has been reported to repress proliferation of epithelial cancer cell lines with IC₅₀ levels of around 60 $\mu\text{mol/L}$ that compare to 27 $\mu\text{g/ml}$ [51].

The inhibitory impact of DOXY and COL-3 in HL-60 cells was reported by Tolemeo *et al.* [52]. They reported the IC₅₀s for DOXY and COL-3 to be 8

$\mu\text{g/ml}$ and $7 \mu\text{g/ml}$, respectively. The results for DOXY were found to be in concurrence with the study, however the IC_{50} for COL-3 was lower in the study. This distinction in IC_{50} can be clarified by various tests and incubation time utilized in the study. The feasibility with resazurin tests was examined, and along these lines analyzed the effects of TCNAs on the metabolic activity of cell mass, while Tolemeo *et al.* assessed the individual cell viability utilizing trypan blue exclusion assay. They likewise reported AC_{50} (condition that is able to induce 50% apoptosis) for DOXY and COL-3 to be 15 and $16 \mu\text{g/ml}$, respectively, although they didn't examine the underlying apoptotic mechanisms. In the study carried out, COL-3 in a concentration of $5 \mu\text{g/ml}$ prompted cell death in HL-60 cells. Other studies that have been published have indicated significant apoptotic and growth inhibitory effects of COL-3 out of a grouping of $10 \mu\text{g/ml}$ in a wide scope of human tumor cell lines and xenografts [53] [54] [55]. TCNAs have been reported to induce apoptosis in different disease cells; be that as it may, the reported biochemical events that underlies the TCNAs-induced cell death differs [56] [57]. The mitochondrion produces energy for a cell and furthermore controls cell death by releasing factors that promote cell death into the cytosol.

1.9. Polyphenols

Polyphenols are an anatomical class of mostly natural (Figure 12), yet synthetic or semisynthetic, natural chemicals portrayed by the evidence of huge amounts of phenol structures. The number and attributes of these phenol structures underlie the one of a kind physical, chemical, and biological properties of specific members of the class. Some examples of this include tannic acid and ellagitanin. The historically essential chemical class of tannins is a subset of the polyphenols [58] [59].

Magnolol and honokiol are phenolic structural isomers that are separated from the bark of Magnolia liliifera that have appeared to strongly hinder the degranulation of RBL-2H3 cells actuated by IgE- antigen complex and additionally the creation of cytokines; IL-4 and TNF- α . In addition, the two compounds

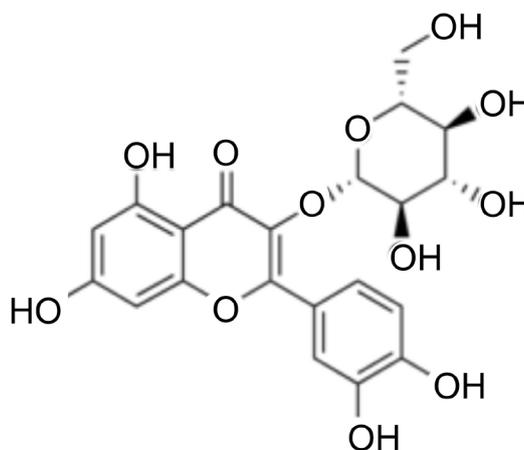


Figure 12. Structure of a plant-derived polyphenol, quercetin-3-*O*-glucoside [60].

powerfully repressed PCA reactions in mice prompted by IgE-antigen complex dose dependently at dosages of 10 and 50 mg·kg⁻¹ [62].

Table 2 shows some of the naturally occurring mast cell stabilizers. Resveratrol, is a phytoalexin, stilbene polyphenolic compound found in grapes, berries and peanuts. It suppresses the presence of inflammatory cytokines, for example, TNF- α , IL-6 and IL-8 in PMACI-induced-HMC-1 cells and diminished the levels of intracellular Ca²⁺ [63]. Similarly, the anti-allergy activity of polydatin, a resveratrol glucoside, fundamentally diminished Fc ϵ RI-mediated degranulation in IgE-sharpened RBL-2H3 cells in a dose dependent way (1 - 100 μ M) and repressed the IgE-dependent PCA response in mice (300 mg·kg⁻¹ [64]. Curcumin

Table 2. Naturally occurring mast cell stabilizers [61].

<i>Source of MC Stabilizers</i>	<i>Compound Name</i>	<i>Mast cell population</i>	<i>Elicitor</i>	<i>In vivo evaluation</i>
Flavonoids	Luteolin	HCMCs	anti-IgE	Unspecified
		BMMCs	Anti-IgE and IL-3	
		Basophils	Antigen	
		RBL-2H3		
	Diosmetin	RBL-2H3	Antigen	Unspecified
	Apigenin	Basophils	Anti-IgE and IL-3	Unspecified
	Quercetin	RBL-2H3 cells	Anti-IgE, Phorbol-12-myristate-13-acetate, calcium ionophore A23187 and PMACI	Unspecified
	Fisetin	RBL-2H3	Anti-IgE, PMACI	Unspecified
		HMC-1	PMACI	
	Kaempferol	RBL-2H3 cells	anti-IgE, phorbol-12-myristate-13-acetate, calcium ionophore A23187 and PMACI	Unspecified
	Ginkgetin	BMMCs	KL	Unspecified
	EGCG	RPMCs	Compound 48/80	PCA reaction in rats
		RBL-2H3 cells		
	Silymarin		Compound 48/80	PCA reaction in rats
Coumarins	Scopietin	RPMC	PMACI	
	Scaporonone		Anti-DNP IgE	PCA reaction in rats
	Artekeiskeanol A	RBL-2H3 cells	Calcium ionophore A23187	Unspecified
	Selinidin		Antigen	Unspecified
	5-Methoxy-8-(2-hydroxy-3-butoxy-3-methylbutyloxy)-psoralen		KL	Unspecified
	Cinnamic acid	RBL-2H3 cells	Antigen	Unspecified
	Ellagic acid		Anti-DNP IgE	PCA reaction in rats
Phenols	Magnolol and honokiol	RBL-2H3 cells	IgE-antigen	PCA reaction in rats
	Resveratrol		PMACI	PCA reaction in rats
	polydatin	RBL-2H3 cells	Anti-IgE	PCA reaction in rats
	Curcumin	RBL-2H3 cells	Antigen	PCA reaction in rats

is a polyphenolic compound found in *Curcuma longa* and related species. Curcumin has exhibited anti-allergic activity in both *in vitro* and *in vivo* models. It fundamentally constrains antigen-induced degranulation in a dosage dependent way (1 - 10 μM) in both RBL-2H3 cells and BMDCs and in addition restrains PCA reactions in mice at 0.5 - 50 $\text{mg}\cdot\text{kg}^{-1}$ dosages. Curcumin fundamentally repressed the expression of mRNA for cytokines; IL-4 and TNF- α in a dose dependent way and additionally their secretion in antigen-stimulated RBL-2H3 cells [63] [65]. The xanthenes; mangostin- α , - β and - γ that are isolated in a sense from the 15onteluk of *Garcinia mangostana* L. inhibited the histamine release from IgE-sensitized RBL-2H3 cells as a response to the antigen through the repression of the signaling transduction pathway including Syk and PLC γ [66].

2. Methodology

The method used to obtain results for this thesis is the utilization of associative thinking and creative synthesis from available literature that seem unconnected to develop a new solution for the treatment of mastocytosis.

2.1. Creative Synthesis

Creative synthesis is a modern solution for solving existing problems and expanding knowledge. The process of creative synthesis is driven by an innovative drive to solve complex problems in fundamental science and engineering for the purpose or getting novel solutions.

Creative synthesis acts like a guide that prompts advancement of thoughts that are results of the synthesis and can be linked with meta-analysis which is essentially consolidating data from various resources and relating the varied factor. In this instance, tetracycline and tetracycline derived compounds is observed for its inhibitory effect on the production of cytokines such as TNA-a which causes inflammation in mastocytosis.

Creative synthesis recognizes and establishes a complex link between previously unrelated concepts. It is not a particular idea; it is more of a new way to understand what an idea is. Synthesis can be characterized as creative because the new pattern involved in it is a novel construction which is distinct from both the dominant understanding (*i.e.* thesis) and alternative perspective (*i.e.* antithesis) [67].

2.2. Process of Ideation from Innovation DNA

The process of creating commercially viable ideas is achieved by making use of certain skills identified in the innovator's DNA, these skills are as follows:

- Observation;
- Questioning;
- Networking;
- Experimenting;
- Associative thinking.

The combination these skills bring about an innovative idea (Figure 13) by making use of the creative skill of an innovator (Figure 14).

The compelling need of this thesis is to find if tetracycline can be used to treat mastocytosis. The questions that are asked as follows:

- What is the cause of mastocytosis?
- How can it be treated?
- How can tetracycline help in mastocytosis treatment?
- Is there a possible combination of tetracycline with other compounds to help improve the treatment?

The data used in this research was obtained from various scientifically published materials such as;

- Scientific publications;
- Text books;

Creative Synthesis

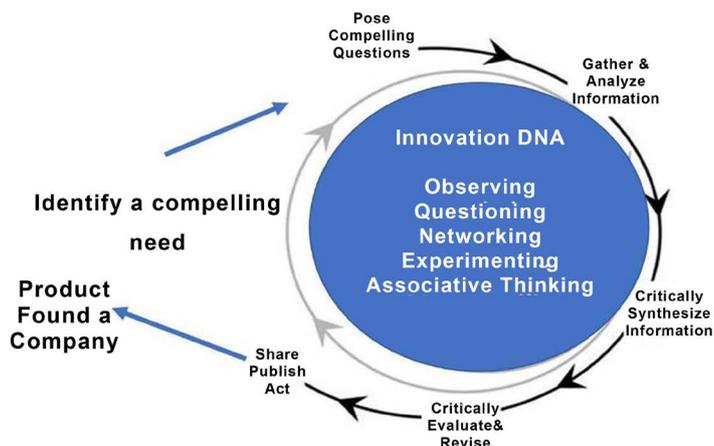


Figure 13. Creative synthesis.

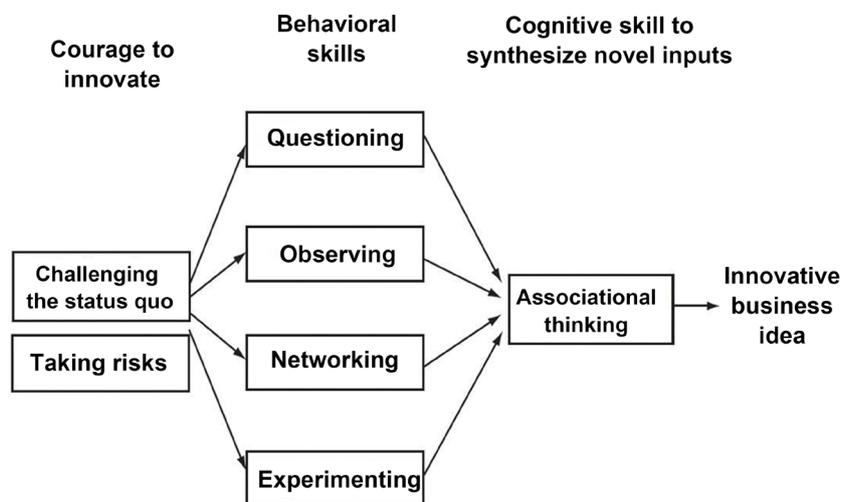


Figure 14. Model shows the creative synthesis skill of an innovator [68].

- Library catalogue;
- Online articles.

The data was selected based on the relevance of the methods that are currently used for the treatment of mast cell diseases and inflammatory related diseases.

3. Results and Discussion

3.1. Chemically Modified Tetracycline

Chemically modified tetracyclines (CMTs) are recently synthesized tetracycline analogues which are without anti-microbial properties and exert a strong anti-collagenase activity. The ability to inhibit the synthesis of nitric oxide (NO), and the expression of NO synthase (iNOS) in j774 cell macrophage is a characteristic that has been shown by most CMTs, which is similar to what is achieved by broad-spectrum antibiotics, doxycycline and minocycline. NO is a short-lived messenger molecule that performs many functions. In contrast, NO acts a dual role of being a physiological intercellular messenger and secondly, can cause cytotoxic activity. It has been demonstrated that NO can induce apoptotic as well as necrotic cell death, depending on the cell type and on its activation status. In programmed cell death (PCD), or apoptosis, one of the earliest and most consistently observed features, is the induction of a series of cytosolic cysteine proteases, known as caspases. A hierarchic model was proposed by D'agostino *et al.* where pro-caspase-8 was activated by an apoptotic stimulus with the liberation of active caspase-8 into the cytosol and, subsequently, the activation of successive effector caspases such as caspase-2, -3, -6 and -7 acting as a proteolytic cascade [69]. Recent evidence suggests that c-myc, in addition to controlling cell proliferation, can also induce apoptosis during the induction of PCD by Fas or in the presence of cytostatic drugs. CMTs have been shown to possess cytotoxic activities against different cell lines, with some that have the ability to cause PCD in targeted cells [69], although the mechanism as to how they act as apoptotic agents is still not clear.

3.2. Mast Cell Stabilizers

Neither ketotifen nor cromolyn are genuine mast cell stabilizers as they don't block inflammatory cytokine discharge. Ketotifen is a histamine-1 receptor enemy that is likewise a weak inhibitor of histamine and prostaglandin discharge through an unknown mechanism. The extra advantage of ketotifen over different antihistamines is that it obstructs the activities of eosinophils generally involved with allergies especially in eosinophilic esophagitis/gastroenteritis. Disodium 18 ontelukast 18 (cromolyn) was believed to be a "mast cell stabilizer" since it blocked rat mast cells, however is an extremely weak inhibitor of human mast cells, and like ketotifen, it hinders histamine and prostaglandin discharge to some degree, but not inflammatory cytokine discharge, again through an unknown mechanism.

NeuroProtek contains luteolin and quercetin, both of which have been ap-

peared to prevent the release of each mediator that have been studied from mast cells. The issue is to get enough of these to be consumed orally. In any case, NP can be given together with either ketotifen and additionally cromolyn to the degree that the latter are useful in a few patients [70].

3.3. Drugs That Interfere with Mast-Cell Symptoms

There is no treatment that brings about in lasting resolution of the skin sores related with cutaneous or systemic mastocytosis. Normal symptoms of cutaneous or systemic mastocytosis are typically tended to through the administration of non-sedating and longer-acting histamine (H1)-receptor antagonist, for example, loratadine (the starting dosage in adults, 10 mg orally day by day; 5 mg orally every day in kids younger than 6 years old; 10 mg orally daily in children that are 6 years old or older), and cetirizine (starting dosage in adults, 5 to 10 mg orally daily; 2.5 mg orally daily in kids younger than 6 years old; 5 to 10 mg orally daily in kids 6 years old or more). Cysteine-leukotriene-receptor antagonists, for example, Montelukast (10 mg orally daily in adults; 4 mg orally once daily in children younger than 6 years old; 5 mg orally daily in kids within the age of 6 and 14 years old) or the 5-lipoxygenase inhibitor zileuton might be helpful when utilized as a part of conjunction with H1-and H2-receptor antagonists [71].

Acetylsalicylic acid (81 to 325 mg orally on once or twice every day in adults) might be gainful in a few patients who have flushing and angioedema (with elevated amounts of urinary prostaglandin D2 or 11β -PGF 2α) if the patient's capacity to get nonsteroidal anti-inflammatory drugs without adverse effects is known. Tricyclic antidepressants (e.g., amitriptyline or doxepine) (25 to 100 mg orally every day depending on the side effect profile in adults) and prochlorperazine (5 to 10 mg orally three or four times daily in adults) might be helpful in light of the fact that they have both histamine H1-receptor antagonism and mast-cell inhibitory properties [72], yet sedation and weight gain diminish the patient's adherence.

Psoralen and ultraviolet A or narrow-band ultraviolet B treatment may reduce the itching and help fade the lesions temporarily [73]. Topical glucocorticoids are for the most part not prescribed, since the lesions typically include substantial body-surface areas.

4. Conclusions

When dealing with mastocytosis, there are 4 major problems to put into consideration and should be analyzed, as seen in **Figure 15**.

With the use of creative synthesis, an innovative solution has to be created which will have to accomplish a couple of things effectively in order to treat mastocytosis completely and they are as follows in **Figure 16**.

The solution will have to be a product that can attack all four of those issues. The addition of CMT will cause apoptosis of the affected cells, then the addition of

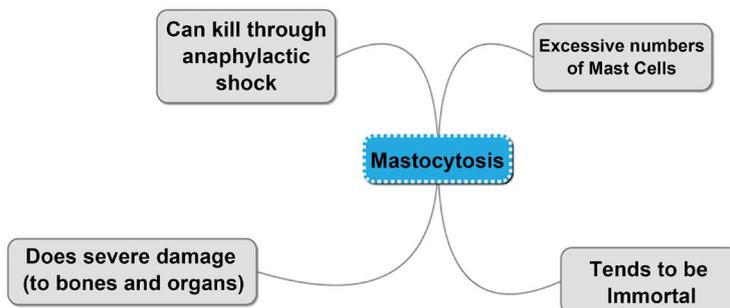


Figure 15. Major problems of Mastocytosis.

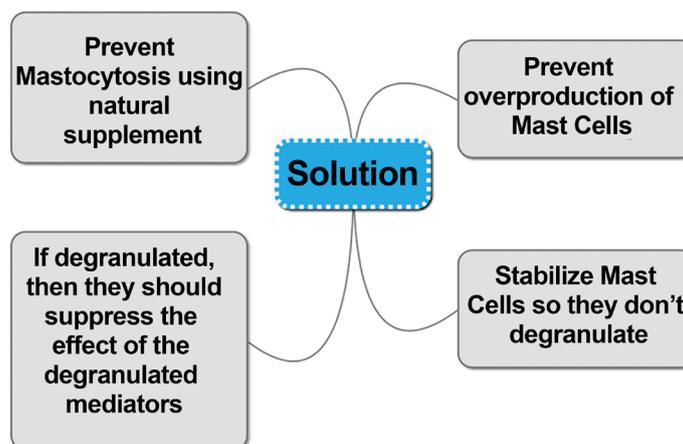


Figure 16. The needs to be met by solution.

other supplements, and compounds that can block the effects of degranulation, or intervene in the histamine release, or cytokine release when the mast cells are de-granulated. This is a complex problem that will be solved with not just one drug but a cocktail of drugs with addition of supplements as well as prescribed drugs.

Most side effects can be dealt with histamine-receptor antagonist or different drugs that disrupt with mast-cell mediators, alongside blockers of mast-cell activation. Patients with aggressive mastocytosis may require extra drugs to interfere with the proliferation and survival of mast cells. Data is currently lacking to distinguish dependable biomarkers of mast-cell activation, signaling steps through which many triggers converge, drugs with double inhibitory activity against mast-cell proliferation and mast-cell activation, and strategies for conveying drugs particularly to mast cells. Treatment of allergic diseases depends on clinically recommended classes of drugs, for example, mast cell stabilizers and H1 antagonists, which control the side effects related with allergic illnesses. The mast cell stabilizer works by stabilizing the mast cell once it has been exposed to an allergen to inhibit the discharge of chemical mediators while H1 antagonists antagonize the histamine at the H1 receptor to dispose of the impacts caused by this bio-genic amine discharged amid an allergic reaction. Despite the fact that the original mast cell stabilizers, for example, DSCG and nedocromil sodium

adequately inhibit mast cell degranulation, the second-generation mast cell stabilizers encapsulated by olopatadine and ketotifen also have anti-histaminic properties which give anti-allergic agent with dual activity.

Be that as it may, the quantity of anti-allergic agents isn't constrained to these drugs in the clinical use. Reports have shown that various compounds which have anti-allergic activity in a panel of *in vitro* and *in vivo* screens have been isolated from the natural sources. In a few circumstances, their instrument of activity isn't exclusively constrained to their impact on mast cells. Without a doubt, as a rule, they likewise target numerous inflammatory events, which may at last supplement their impact on mast cell degranulation. Additionally, a large number of these anti-allergic operators are sourced from foodstuffs, for example, the flavonoid family which enters the body every day where they could possibly target activated mast cells and lessen the mast cell response to allergens.

Various mast cell stabilizing compounds have been recognized in the most recent decade from; natural, biological and engineered sources to drugs as of now in clinical uses for different indications. Despite the fact that as a rule, the exact method of activity of these molecules is unclear, these substances have shown mast cell stabilization activity and therefore may have a potential remedial use in the treatment of allergic and related diseases where mast cells are characteristically included. In any case, owing to the heterogeneity of the mast cell, and their molecular targets, the genuine capability of any new mast cell stabilizer must be acknowledged once its properties are assessed in an extended scope of preclinical *in vitro*, *ex vivo* and *in vivo* models of efficacy and toxicity [61].

Potential for CMT's and Polyphenols to Overcome Shortcomings

CMTs are still in their earliest stages with respect to use in humans, for instance, the weaknesses of CMT such as the over the top suppression of MMPs which may disrupt the ordinary physiologic turnover of collagen. The question is would we be able to find the right combination or other dynamic compounds to overcome the deficiencies of CMT's. Tetracycline and its derivatives provide an advantage of MMP interaction, inhibition of MMP tissue, cytokine and growth factors.

They influence the succession of inflammation with an implication on immunomodulation, cell multiplication and angiogenesis; these activities improve their scope in treating a wide scope of disease entities. Non-antimicrobial CMTs retain their diverse activities in the organ systems. These activities include: anti-inflammatory, anti-proteolytic actions, anti-apoptotic, the inhibition of angiogenesis and tumor metastasis. A range of biological actions of CMT's in dermatitis, periodontitis, atherosclerosis, cancer, diabetes, arthritis, inflammatory bowel disease, malignancy and prevention of bone resorption as found mastocytosis is especially important to future disruptive discoveries in minocycline-like treatments, of which Quercetin is an example.

The pro-anabolic, anti-inflammatory and the anti-catabolic actions that sum

up the non-antimicrobial characteristics of CMTs, make them a powerful pharmaceutical against chronic inflammatory disease management. The excessive inflammatory reaction to a trigger caused by an antigen in periodontitis and other chronic inflammatory disease can lead to the progression of the illness to an autoimmune disease. However, their adjunctive use in managing periodontitis and illnesses like mastocytosis could have a very beneficial effect in controlling the excessive inflammatory substance release.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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