



Plant Histaminase as Bioactive Agent to Lower the Histamine Level: A Mini-Review

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Abstract

Histamine is a biogenic amine originating endogenously or exogenously from Histidine by enzymatic decarboxylation. Endogenous histamine is mostly generated by basophils and mast cells that, when activated, will release histamine that is involved in various regulatory processes but also will induce multiple allergic effects (hypotension, tachycardia, vascular risks) including anaphylactic shock and possible death. For some histamine related symptoms (itching, asthma, hyperacidity), there are antihistaminic drugs (e.g. Desloratadine-Aerius®, Loratadine-Claritin®, Ranitidine-Zantac®) whereas for anaphylaxis, epinephrine (EpiPen®) is required. Exogenous histamine, frequently associated to fermented food and beverages, some fruits, fish, may induce a food histaminosis and trigger pseudo-allergic phenomena for which there is no current treatment available. Histamine may also exert some pro-inflammatory effects, particularly damaging for subjects with Inflammatory Bowel Diseases (IBD) as Crohn's Disease (CD) and Ulcerative Colitis (UC), mostly treated with anti-inflammatory drugs. Histamine deleterious effects and those produced as side-effects of antihistaminic drugs (allergic phenomena) or of anti-inflammatory drugs are inconvenient (nausea, diarrhea, dizziness).

For this reason, novel enzymatic strategies with Diamine Oxidase (DAO, histaminase) to decrease the histamine levels in allergic reactions to food and in ulcerative colitis were recently proposed. This may alleviate the symptoms associated with IBD and food allergens. The therapeutic concept is that histaminase will decrease the level of histamine in the intestine by oxidation, involving the dissolved oxygen. Since the by-product of the DAO reaction is hydrogen peroxide (H₂O₂), a pro-oxidant agent generating undesirable oxidative damaging effects, a combination of catalase and vegetal histaminase in tablet formulations for oral administration was proposed. Catalase will decompose H₂O₂ generating *in situ* more oxygen, promoting thus the decomposition of histamine under histaminase action. Thus, the dual enzymatic histaminase + catalase tablets, could contribute to a healthier intestinal mucosa. This DAO approach seems a non-toxic way to improve the treatment IBD and related inflammatory pathologies.

Keywords

Histamine, Diamine Oxidase (DAO, Histaminase), Catalase, Inflammatory Bowel Diseases (IBD), Food histaminosis, Lower intestine and Colon delivery

Introduction

Histamine is a biologically active molecule: a biogenic amine generated by the alpha-decarboxylation of the amino acid histidine by histidine decarboxylase. This biogenic amine is widely distributed and is involved in various important biological processes (regulation of gastric acidity, activity of smooth muscles as well as inflammatory and immunological reactions) through the activation of one or more of the four specific histamine receptors H₁, H₂, H₃, H₄ on target cells [1,2]. In general, H₁ and H₂ receptors are present in the vascular smooth muscle cells (SMCs) and endothelial cells, H₃ and H₄ receptors

are mostly expressed in central nervous system and in the enteric nervous system and H₄ is expressed in bone

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marrow, liver, lung, spleen, small intestine and colon.

Histamine: friend & foe and its signalling issues

Histamine can act as vasodilator and as vasoconstrictor of smooth muscle such as uterine and gut smooth muscle [3-5]. As a vasoactive biogenic amine, histamine is able to act on H1-H4 receptors activating the G protein and trigger signals modulating vasomotricity. Histamine may strongly increase vascular permeability and regulate the blood pressure. Histamine may also induce tachycardia and arrhythmias depending on the activated receptor and location of target cells [6]. Furthermore, histamine also mediates neurotransmission in the central nervous system [7], immunomodulation [8], hematopoiesis [9],

cell proliferation [10], angiogenesis in tumour models i.e., adenocarcinoma of stomach or large bowel [11-13]. It also promotes mucosal and gastric acid secretion. As a constrictor of smooth muscle, histamine activates H1 receptors located on SMCs (smooth muscle cells) inducing peristalsis [2,14].

Origin of histamine

Endogenous origin: Histamine is produced by the organism itself and is present in many tissues. Histamine is mostly generated in gastric enterochromaffin-like (ECL) cells, histaminergic neurons, basophiles and mast cells [15,16] which store it in intracellular vesicles (Figure 1). Histamine is released as result of allergens and other ex-

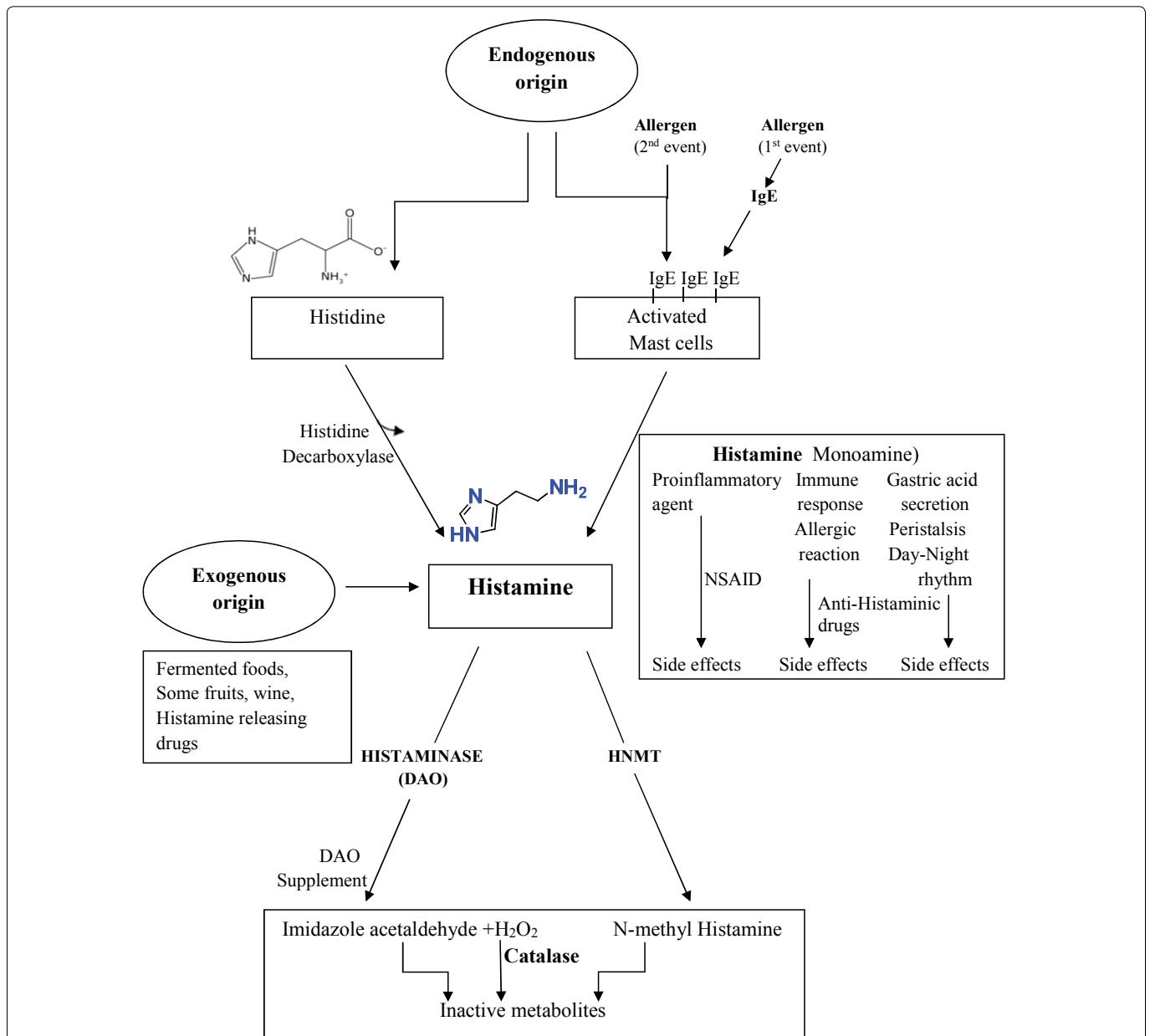


Figure 1: Schematical presentation of endogenous and exogenous generation of histamine. Endogenous histamine is generated by histidine decarboxylation and in allergic events, degranulation of mast cells releases large (risky) amounts of histamine (possible treatment with antihistaminic drugs). Oral DAO (histaminase) supplements may limit inconvenient food-histaminosis and the damaging effects of histamine-related dysfunctions [71].

ogenous factors. For instance allergens, at a first allergic event, will trigger specific antibodies (IgE) that will rapidly act on basophiles and on mast cells. At a subsequent allergic event, the allergen will be recognised by the IgE antibodies retained by the basophil and mast cells inducing degranulation of histamine vesicles with histamine release, which will induce drastic allergic phenomena (Figure 1). Besides allergens, mast cells degranulation may also be mediated by non-immuno stimuli such as neuropeptides [17], hyperosmolarity [18], lipoproteins and platelet activating factor [19], adenosine [20]. In addition to these mechanisms, various medications and many agents such as opiates [21,22], muscle relaxants [23] plasma expanders and radiocontrast materials [24] as well as physical factors (i.e. extreme temperature, vibrations) [25,26] can be responsible of histamine release. All these mentioned allergens, chemical and physical factors are responsible of deleterious histamine able to induce allergic phenomena including anaphylactic shock and possibly death.

Most recent knowledge on histamine functions was acquired in the last decade. Histamine is normally catabolized by copper diamine oxidase (DAO) and FAD (Flavin-Adenine-Dinucleotide) monoamine oxidase (MAO) and also by histamine N-methyltransferase (HNMT). These enzymes are localized at cellular level, but histamine is unable to easily enter the intracellular space except when the transport is mediated by organic cationic transporters (OCT) as described by [27] Ogasawara, et al. The OCT facilitate in and out processes from extracellular space into the cells and from cells to plasma or other external fluids (Figure 2). For instance the access of biogenic amines (as cationic agents) from plasma into the cells can be mediated by OCT. Thus histamine may be converted in products that will be eliminated (Figure 1 and Figure 2). Histamine not metabolised can be eliminated via OCT into the intestinal lumen. Cannot be excluded the access of exogenous histamine via OCTs disposed on Enterocyte's tight junctions. In this case, an excess

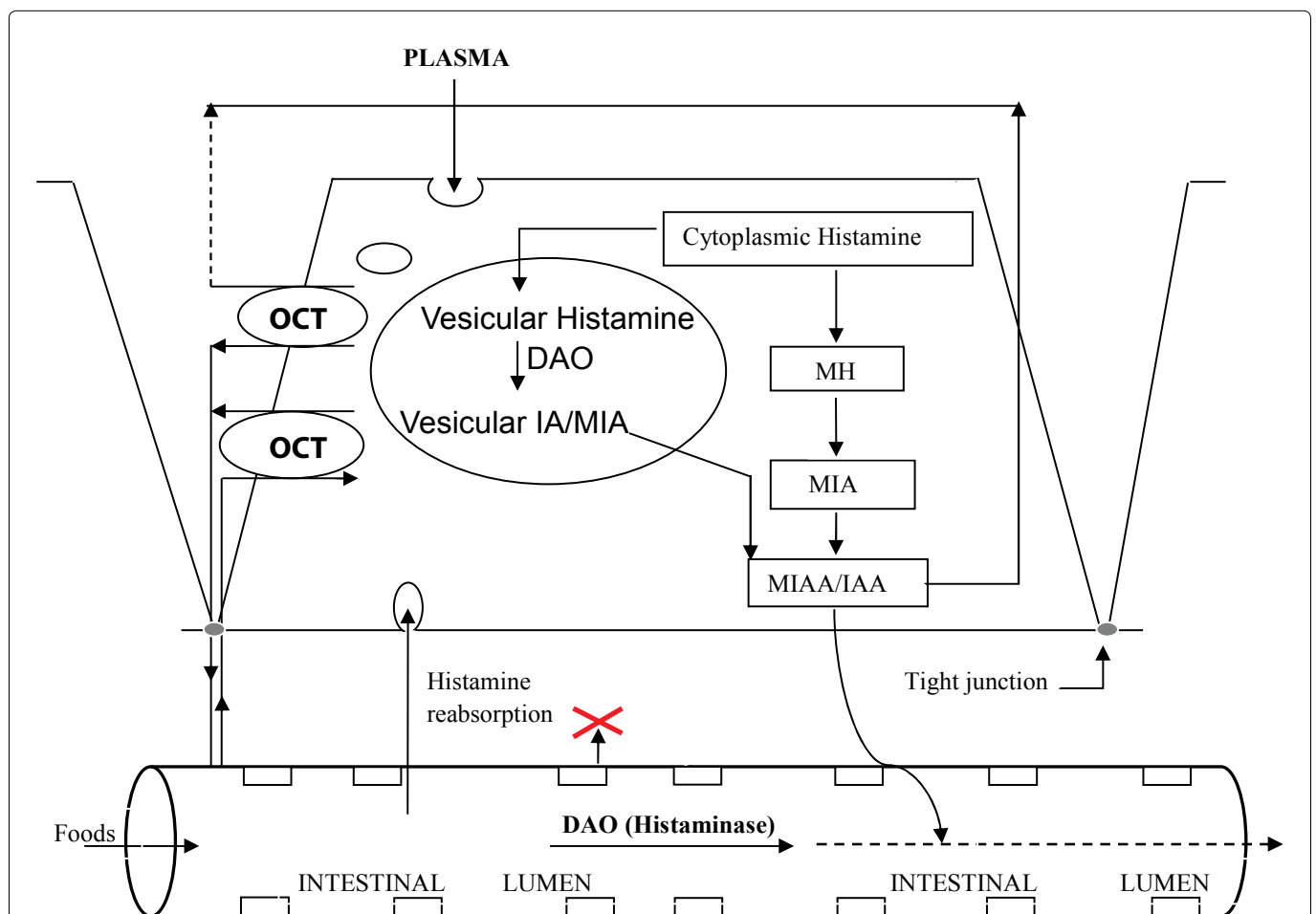


Figure 2: Hypothetical presentation of histamine bioelimination by orally administered DAO and catalase. Histamine from plasma is up taken by enterocytes via OCT (Organic Cationic Transporters) and may be catabolized by vesicular DAO (Diamine Oxidase) and MAO (Monoamine Oxidase) or by HNMT (Histamine Methyl Transferase) to form IA (Imidazole Acetaldehyde), MIAA(1-Methyl-4-ImidazoleAcetic Acid), IAA (Imidazole-4-Acetic Acid), MH (Methyl-Histamine) or is eliminated by enterocyte's tight junction in intestinal lumen with possibility of reabsorption (via OCT) by enterocyte cells for further catabolism [56]. Orally administered DAO may decompose Histamine and the re-uptake is thus prevented.

of histamine histamine may be a risk for pseudoallergic phenomena.

Exogenous origin: Histamine may often be present in certain foods, particularly fish, cheese, dairy products, some fruits and fermented food items (some wines, beers, sauerkraut [6,28,29]. It is almost impossible to remove histamine present in food through freezing or cooking [15]. This ingested exogenous histamine can generate a condition called food histaminosis and the symptoms are similar to those induced by allergenic factors; this is why food-histaminosis is considered as a pseudo-allergy with duration of 3-4 days and for which there is no current treatment.

Amine oxidases and physiological catabolism of histamine

The diamine oxidase (DAO, also known as Histaminase), is a copper-enzyme (EC 1.4.3.22) present in different tissues (kidney, placenta) and In intestinal mucosa where is abundant [30]. It regulates cells proliferation via degradation (oxidative deamination) of polyamines (known to be involved in control of protein synthesis, growth, differentiation and cells proliferating mechanism [31,32]. DAO also inactivates the endogenous and exogenous excess of dietary histamine preventing “pseudo-allergic” reactions such as food histaminosis (Figure 2).

Histamine can be metabolised principally by two processes, via oxidative deamination by DAO copper-enzyme or by monoamine oxidase (MAO, a FAD-enzyme) and via histamine N-methyl transferase (HNMT) by histamine methylation [6,33,34]. These mechanisms depend on the localisation of histamine and generate different end products. Stored in secretory granules structures associated to plasma membrane of cells, DAO protein is released in circulation via heparin and by immunity stimulation inducing degranulation. DAO activity is elevated in intestinal mucosa and villousities, kidney and placenta [6,35]. HNMT is a cytosolic enzyme which inactivates intracellular histamine [15].

Intoxication with histamine: It is a food histaminosis caused by ingestion of a high content of histamine [15,36]. Common symptoms of histaminosis include headache, arrhythmia, tachycardia, nausea, anxiety, abdominal cramps, diarrhea and nasal congestion. Other conditions such as reduction of diamine oxidase activity or the presence of factors inducing degranulation of mast cells can also increase histamine toxicity. For instance, in the case of scombroid fish poisoning, in addition to the high level of histamine, the decomposition process of fish may also release other biogenic amines (cadaverine, putrescine) which can further potentiate toxicity through inhibition of intestinal diamine oxidase [15,37]. In addition to histamine-rich foods, many other foods may increase histamine release via allergenic factors by

mast cells degranulation (Figure 1) and/or inhibition of DAO activity. A fragility of duodenal mast cells with elevated degranulation and histamine release was shown in subjects with pseudo allergic history [6].

Role of histamine in enteric dysfunctions

In gastrointestinal tract, histamine is involved in various physiological processes such as inflammatory responses, regulation of intestinal motility and gastric acid secretion [38,39]. It is also implicated in gastrointestinal ailments such as gastric ulcers, Inflammatory Bowel Diseases, ulcerative colitis and food allergies [2].

Histamine and gastric acidity - Due to stimulation by mediators (including histamine and gastrin), parietal cells of stomach secrete gastric acid (hydrochloric acid, pH 1.2-3.8), with the role to solubilize ingested foods and to induce the release of pepsin [40,41]. Histamine released from ECL cells, stimulates gastric acid secretion through activation of histaminic receptors H2 on parietal cells [2,42,43]. Histamine may contribute to the formation of duodenal ulcers by increasing gastric acid release [44,45]. Receptors H2-antagonists are able to inhibit gastric acidity and are used in treatment of peptic ulcers [46-48].

Histamine as mediator of acute inflammatory response - On the endothelium, the histamine-activation of H1-receptors stimulates PLC (Phospholipase C), the key enzyme responsible for the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) to 1,2-diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) intracellular messengers. The DAG stimulates protein kinase C (PKC) implicated in vasoconstriction, and IP3 triggers the release of calcium (Ca²⁺) ions from reticulum endoplasmic to cytosol [49] forming calcium/calmodulin complexes and activating endothelial nitric oxide synthase (eNOS) [50]. The nitric oxide (NO) binds to the sGC (sodium Guanylyl cyclase) increasing the level of cGMP and vasorelaxation. The NO is also oxidized to peroxynitrite anions (ONOO⁻), which stimulates nuclear factor kappa B (NFkB) to (pro) inflammatory mediators and enhances cyclooxygenase-2 (COX-2) prostaglandins and thromboxane A2 (TX2).

Histamine intolerance: Histamine released from granulocytes and transported in blood stream is usually rapidly inactivated. This mechanism is effective in healthy body but can be disrupted by: i) a strong release of histamine (histamine intoxication) and ii) a low activity of the DAO due to some food contents (biogenic amines) as well as enteric dysfunctions (i.e. intestinal inflammatory conditions and damaged enterocytes, known as related to a low level of DAO). Low DAO activity can also be due to genetic predisposition [15].

Drugs-induced histaminosis: Some drugs have the capacity to inhibit the DAO activity or favour the release of histamine and enhance histamine intolerance [6,51-53].

Inflammatory bowel diseases and current treatment: IBD is a group of disorders (Crohn's disease, Ulcerative colitis) characterised by severe inflammation and potential ulceration of sections of the gastrointestinal tract. In Crohn's disease the inflammation commonly affects the small intestine and/or colon but may attain any area of gastrointestinal tract from mouth to anus. In ulcerative colitis the inflammation is mostly limited to the colon. Both can increase the risk of colorectal cancer. Degranulation and number of mast cells is strongly increased in mucosa of the ileum and of the colon of patients with IBD [54,55].

Histamine released from mast cells and that eliminated from plasma via OCT [27,56] as well as that from food intake may enhance the inflammation level and markedly contribute to severity of IBD [55]. Anti-inflammatory drugs as 5-aminosalicylic acid (5-ASA, mesalazine), corticosteroids, NSAID (non-steroidal anti-inflammatory drugs), immune-suppressor drugs (infliximab, cyclosporine, azathioprine) and antibiotics are currently used for IBD treatment [57]. Furthermore, certain drugs have side's effects such as loss of sense of smell, drowsiness, nausea, vomiting, dizziness and urinary disorders. Some vegetal supplements as curcumin [58,59], Cissampelos glaberrima [60] and recently cannabis [61,62] were found to produce significant clinical benefits to patients with IBD, without side effects. These treatments reduce symptoms, may provide remission for various durations, but still not afford complete recovery (cissaglaberrimine and trilobinine-two alkaloids) are plant antihistaminic.

It is worth to note that in gastrointestinal diseases including Crohn's disease and ulcerative colitis, the level and activity of Diamine oxidase is reduced, leading to a lower degradation and accumulation of histamine (pro-inflammatory factor) [63-65].

Novel Approach of Histaminase: Catalase in Treatment of IBD

The premises of the novel approach are: a) In IBD, the level and activity of Diamine oxidase is reduced, leading

to a lower degradation and accumulation of histamine as pro-inflammatory agent [63,65] b) Current treatments target histaminic receptors to reduce allergic effects but cannot reduce the level of histamine in the intestinal lumen; c) An oral Pig-Kidney DAO supplement is commercially available as Histame[®] or DAOSIN[®] capsules recommended for food histaminosis and histamine-related intestinal dysfunctions [66].

Recently, a novel approach [67,68] was proposed to treat histamine-related dysfunctions with a vegetal DAO extract from White Pea (*Lathyrus sativus*). Another recent study on vegetal DAO alone or in combination with catalase, showed that H₂O₂ produced by DAO and histamine at concentrations higher than 1 mM is toxic to the Caco-2 cells and that in the presence of catalase, the DAO-induced increase of histamine toxicity was abolished [69]. These results support the hypothesis that adding catalase to formulation of DAO will protect against H₂O₂ produced by DAO (H₂O₂ may act as pro-oxidant). Catalase is a homo-tetrameric enzyme (EC 1.11.1.6) able to rapidly decompose H₂O₂ [70].

The novel approach of oral administration of combined DAO and catalase (Figure 3) appears of interest for the treatment of food histaminosis and of histamine-related enteric dysfunctions and also to ameliorate the treatment of IBD: Crohn's disease (particularly ileocolitis, jejunoileitis) and ulcerative colitis [67,71]. Concerning the ammonia by-product of DAO generated during the oxidative desamination it is known that it may play various deleterious effects as Neurotoxic [72] and as an agent causing colon mucosal cell damage [73]. Further studies are needed to evaluate the amounts of NH₃ released following the administration of DAO pills related to the amount generated by intestinal bacteria and that eliminated (intestinal absorption and by feces). This approach based on a vegetal DAO associated to Catalase is now in development and the bioactive enzymes will be formulated for oral administration as monolithic tablets conceived for lower intestine and colon delivery [66,67,74].

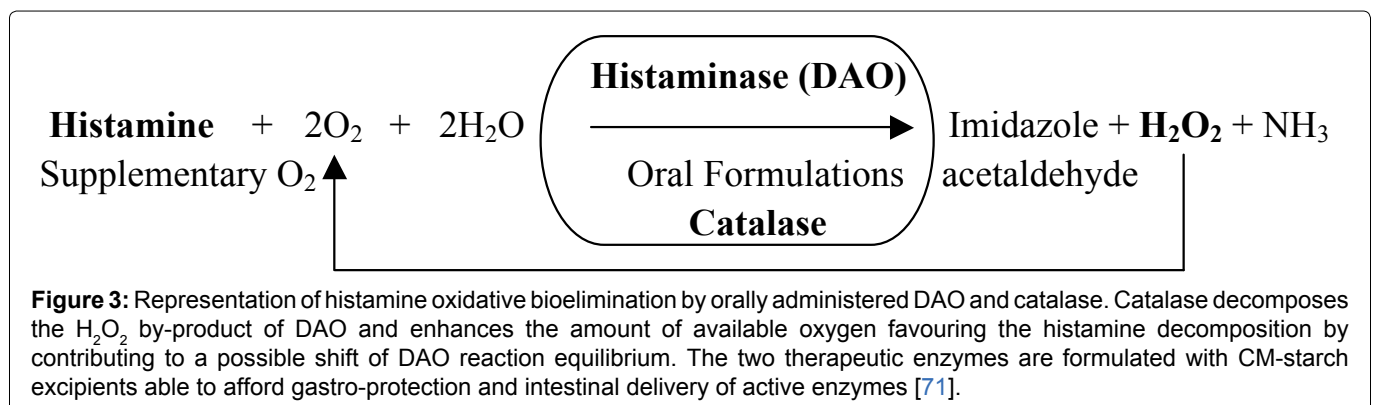


Figure 3: Representation of histamine oxidative bioelimination by orally administered DAO and catalase. Catalase decomposes the H₂O₂ by-product of DAO and enhances the amount of available oxygen favouring the histamine decomposition by contributing to a possible shift of DAO reaction equilibrium. The two therapeutic enzymes are formulated with CM-starch excipients able to afford gastro-protection and intestinal delivery of active enzymes [71].

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