

# Nutra-Hist



## Applications

- Healthy Immune Response Support
- Healthy Inflammatory Response Support

## Introduction

**NutraMedix Nutra-Hist** includes herbs from traditional health practices with diverse mechanisms of action: **stinging nettle leaf** (*Urtica dioica*), **perilla seed** (*Perilla frutescens*), **lemon balm leaf** (*Melissa officinalis*), **black cumin seed** (*Nigella sativa*), **Baikal skullcap root** (*Scutellaria baicalensis*), **turmeric root** (*Curcuma longa*), and **noni fruit** (*Morinda citrifolia*).

**NutraMedix Nutra-Hist** is made at our U.S. facility using a proprietary extraction process that optimizes the constituents of the herbs in their original, unprocessed state to achieve broad-spectrum concentration. Because NutraMedix's extracts are made in our own facility, we control all aspects of quality, including stringent ID testing, microbial testing, and heavy-metal testing. NutraMedix rigorously follows current good manufacturing practices (cGMP), as do our suppliers.

## Healthy Immune Response Support

Th2 cytokines IL-4 and -5 promote Th2-mediated immune responses and support IgE production, activating mast cells and causing them to release their contents, including histamine. When histamine binds to its receptors, it triggers signaling pathways that involve NF-kappaB, a transcription factor that regulates COX-2 and

iNOS. These enzymes generate prostaglandins and nitric oxide (NO), which contribute to immune signaling and inflammatory response. Blocking histamine receptors such as H1, H2, or H4 helps reduce the effects of histamine and limit further release of mediators such as cytokines, prostaglandins, and leukotrienes.

Research suggests that certain bioactive compounds may influence histamine receptor activity and Th2-mediated pathways involved in IgE-associated responses. These compounds are being studied for their potential to help maintain balanced mast cell activity and normal immune function, supporting healthy immune and healthy inflammatory responses.

**Stinging nettle leaf** may help with immune support. Proposed mechanisms include maintaining histamine receptor activation, tryptase levels, and COX-1 and COX-2 levels already within the normal range.<sup>1</sup> Normal tryptase levels also help facilitate normal mast cell stability.<sup>2</sup> In a double-blind, placebo-controlled trial, 40 participants with seasonal allergies were randomly assigned to take a stinging nettle tablet or a placebo, daily for one month. At the end of the study, participants in the stinging nettle group experienced significant support for healthy nasal function and normal eosinophil levels, without significant changes to IgE, IL-4 or IL-5 levels.<sup>3</sup>

**Perilla seed** may help with immune support. In a controlled trial, 128 children were randomly assigned to the perilla supplement group (perilla

seed with quercetin and vitamin D3) or the control group (no treatment) for 4-12 weeks. Researchers found that children in the perilla seed group had significantly improved nose and eye comfort, compared to the control group.<sup>4</sup> In an open clinical study, 23 participants with a history of allergies were given the same perilla seed supplement, daily for one month. Comfort was measured at baseline and at the end of the study. Participants experienced a 70% improvement in nose and eye comfort.<sup>5</sup>

The different aerial parts of perilla contain the same or similar constituents, although in varying amounts. Perilla seed has a high phenolic content, of which most is rosmarinic acid, while perilla leaf has the highest flavonoid content.<sup>6</sup> In a double-blind, placebo-controlled, parallel group study using perilla leaf extract standardized to 20% rosmarinic acid, 30 participants with pollen allergy were randomly assigned to perilla leaf 200 mg, perilla leaf 50 mg, or a placebo, daily for 21 days. At the end of the study, the perilla group was able to maintain nasal eosinophil and neutrophil levels already within the normal range, along with significant support for nose and eye comfort.<sup>7</sup> In the 200 mg dose group, 70% of participants reported significant improvements in nose and eye comfort, compared with 55.6% of participants in the 50 mg dose group and only 30% of participants in the placebo group.<sup>7</sup>

In a mouse model, Perilla leaf ethanolic extract helped maintain IL-5, IL-13, and IgE levels already within the normal range.<sup>8</sup> Researchers concluded that perilla extract helped maintain Th2 responses and airway comfort already within the normal range.<sup>8</sup> In another mouse study, perilla leaf extract helped maintain skin comfort.<sup>9</sup> One in vitro study showed that perilla leaves helped support mast cell stability,<sup>10</sup> and another showed that perilla leaf extract helped maintain IL-4, IL-5, and IL-13 cytokines already within the normal range.<sup>11</sup>

**Lemon balm leaf** may help with immune support.<sup>12</sup> In vitro studies have shown that lemon balm leaf methanolic extract may help maintain hyaluronidase levels already within the normal range, which helps prevent hyaluronidase from breaking down into hyaluronic acid, supporting mast cell integrity as well as a healthy inflammatory response.<sup>12</sup>

**Black cumin seed** may help with immune support.<sup>13</sup> In a double-blind, placebo-controlled trial, 65 participants ages 18 to 60 were randomly assigned

to take black cumin seed oil containing 5% thymoquinone, twice daily after food for 15 days. Compared to the placebo group, the black cumin seed group experienced significant support for both nasal and eye comfort.<sup>13</sup> In a mouse study, mice given black cumin seed or its constituent thymoquinone experienced support for healthy intestinal mast cells.<sup>14</sup> In a rat study, black cumin seed supported peritoneal mast cell stability as well as histamine levels already within the normal range.<sup>15</sup> Another rat study showed that black cumin seed oil, thymoquinone, and nigellone helped maintain 5-lipoxygenase (5-LOX) synthesis already within the normal range.<sup>16</sup>

**Baikal skullcap root** may help with immune support.<sup>17</sup> In a study with ex vivo human nasal tissue, Baikal skullcap root helped maintain histamine and prostaglandin levels already within the normal range and helped support mast cell stability.<sup>17</sup> It may help maintain Th1, Th2, and Th17 cytokines already within the normal range.<sup>17</sup> In addition, it may help with late-phase immune support by maintaining IL-5 already within the normal range.<sup>17</sup>

In a mouse study, the mice were given either Baikal skullcap root or its constituent wogonin for 16 days. Baikal skullcap helped maintain IgE, IL-4 and IL-5 already within the normal range.<sup>18</sup> Wogonin helped maintain IL-4, as well as interferon gamma, already within the normal range.<sup>18</sup> Both skullcap and wogonin helped maintain normal Th2 immunity, particularly IgE and IL-5 levels.<sup>18</sup>

**Turmeric root** may help with immune support.<sup>19</sup> In mice given curcumin, the main ingredient of turmeric root, curcumin helped maintain mast cell stability, NF-kappaB activation, and Th2 responses (including IL-4 and IL-5) already within the normal range, supporting normal food tolerance.<sup>19</sup> In another mouse study, turmeric root was shown to help maintain normal Th1/Th2 balance and support normal food tolerance.<sup>20</sup> In a guinea pig study, curcumin helped maintain IgE, IL-4, and NO already within the normal range, helping maintain nose and eye comfort.<sup>21</sup> An in silico study showed that curcumin is able to bind to H1 receptors.<sup>22</sup> Curcumin is known to maintain TNF-alpha and IL-4 levels already within the normal range and helped maintain bone marrow mast cell stability in mice.<sup>23</sup>

**Noni fruit** may help with immune support.<sup>24</sup> In a study with mice, fermented noni fruit helped maintain histamine and IgE levels, as well as Th1-,

Th2-, Th17-, and Th22-mediated cytokine levels already within the normal range.' In addition, it helped support normal skin barrier proteins and maintain skin comfort.<sup>24</sup> In another mouse study, a 50% ethanolic noni fruit extract helped with both early- and late-phase immune support, maintaining skin comfort.<sup>25</sup> An additional mouse study showed that deacetylasperulosidic acid (DAA), a main ingredient in fermented noni, helped support mast cell stability and helped maintain histamine levels already within the normal range, supporting normal skin barrier function.<sup>26</sup>

## Healthy Inflammatory Response Support

**Stinging nettle leaf** may help with healthy inflammatory response support.' In a double-blind, placebo-controlled trial, 69 participants were randomly assigned to stinging nettle leaf or a placebo. At the end of the study, 48% of the stinging nettle group rated stinging nettle as equal to or better than the positive control, compared to 21% of the placebo group.<sup>27</sup> Proposed mechanisms include helping maintain histamine receptor activation, tryptase levels, and COX-1 and COX-2 levels already within the normal range.<sup>1</sup>

**Perilla seed** may help with healthy inflammatory response support.' Studies suggest that perilla seed may help maintain levels of COX-2, TNF-alpha, and interleukins IL-1beta, IL-6, and IL-8 already within the normal range.<sup>28</sup> It may also help maintain NF-kappaB signaling already within the normal range.<sup>28</sup> In addition, studies have shown that perilla seed flavonoids help maintain vascular permeability already within the normal range, and the constituent luteolin has been shown to help maintain inducible nitric oxide synthase (iNOS) already within the normal range.<sup>28</sup> The constituent apigenin helps maintain COX-2, TNF-alpha, and iNOS levels already within the normal range.<sup>29</sup>

**Lemon balm leaf** may help with healthy inflammatory response support.' In a study with rats given either lemon balm leaf hydroalcoholic extract or the phenolic acid constituent rosmarinic acid, both helped support a healthy lung inflammatory response.<sup>30</sup> Studies suggest that lemon balm helps maintain NF-kappaB signaling and associated cytokines already within the normal range.<sup>31</sup>

**Black cumin seed** may help with healthy inflammatory response support, attributed to the constituent thymoquinone, which helps maintain NF-kappaB activation and pro-inflammatory gene expression for COX-2, TNF-alpha, IL-1beta, and IL-6 already within the normal range.<sup>32,33</sup>

**Baikal skullcap root** may help with healthy inflammatory response support.' Studies suggest that the constituent baicalin helps maintain NF-kappaB signaling along with TNF-alpha, iNOS, and COX-2, already within the normal range.<sup>34</sup> It also helps maintain interleukins IL-1beta, IL-6, and IL-8 already within the normal range, along with Th17 cells already within the normal range.<sup>34</sup> In a rat study, Baikal skullcap root given daily for 24 days helped maintain a healthy inflammatory response and support joint comfort.<sup>35</sup>

**Turmeric root** may help support a healthy inflammatory response.' The constituent curcumin may help maintain NF-kappaB, STAT3, Nrf2, ROS, and COX-2 already within the normal range, supporting a healthy inflammatory response.<sup>36</sup> In a systematic review and meta-analysis of 66 randomized, controlled trials, researchers found that turmeric root and/or curcumin may help maintain C-reactive protein, TNF-alpha, and IL-6 already within the normal range.<sup>37</sup> Turmeric root also helps maintain Th17 cells already within the normal range.<sup>38</sup>

**Noni fruit** may help support a healthy inflammatory response, as seen both in vitro and in vivo.<sup>39</sup> Noni may help maintain phase II enzyme function already within the normal range through the support of quinone reductase (QR), supporting a healthy inflammatory response by promoting normal cell signaling.<sup>40</sup> Noni fruit may also help maintain TNF-alpha, 5-LOX, and Nrf2 levels already within the normal range.<sup>41-43</sup>

Constituent flavonoids such as quercetin and kaempferol may contribute antioxidant activity to support a healthy inflammatory response.<sup>39</sup> Constituent flavonoids may also help maintain histamine release, leukocyte migration, PGE<sub>2</sub>, and LTB-4 already within the normal range.<sup>42</sup> In addition, flavonoids may help maintain IL-2 secretion and T-cell proliferation already within the normal range via MAPK and phospholipase-C pathways.<sup>42</sup> Constituent iridoids may help maintain COX-1, COX-2, PGE<sub>2</sub>, and nitric oxide (NO) already within the normal range.<sup>39,40,42</sup>

A noni fruit heteropolysaccharide was found to support a healthy inflammatory response, in vitro and in vivo, via multiple mechanisms maintaining leukocyte migration, nociception, and bradykinin levels already within the normal range.<sup>44</sup>

Noni fruit was comparable to a positive control in maintaining metalloproteinase 9 (MMP-9) already within the normal range in human monocytes, and was comparable to a positive control for comfort in a study with mice, validating centuries of ethnobotanical use for healthy inflammatory response support.<sup>43</sup> Noni may also help maintain levels of high-sensitivity C-reactive protein (hsCRP) already within the normal range.<sup>45,46</sup> In RAW 264 cells, noni helped maintain NF-kappaB activation already within the normal range.<sup>47</sup>

## Other Support

### Mood Support

According to a meta-analysis of randomized, controlled trials, **lemon balm leaf** helped support a healthy mood in participants experiencing everyday stress or occasional low mood, compared to placebo.<sup>48</sup> In a double-blind, controlled study, 90 healthy participants ages 50–69 were randomly assigned to **turmeric root** extract or a placebo, daily for 12 weeks. At the end of the study, compared to the placebo group, the turmeric root group maintained mental-emotional wellness.<sup>49</sup> Results from a preclinical mouse study suggest that **noni fruit** may maintain a healthy mood by supporting GABA<sub>A</sub>ergic, adrenergic, and serotonergic systems.<sup>50</sup>

### Gastrointestinal Support

A rat study showed that **stinging nettle leaf** extract helped with gastrointestinal tissue support.<sup>51</sup> In an ex vivo study, a hydroethanolic extract of **lemon balm leaf** showed calming support of gastroin-

testinal activity.<sup>52</sup> Compounds from **turmeric root** showed support for H4 blocking, and may offer support in the gastrointestinal tract.<sup>53</sup> In a preclinical study with polyphenols from **noni fruit** under simulated digestion, noni polyphenols had beneficial effects on the gastrointestinal microbiome.<sup>54</sup>

### Neurological Support

In preclinical studies with baicalin from **Baikal skullcap root**, researchers have noted neuroprotective support and the need for more studies.<sup>55</sup> Brain histamine levels help support normal microglial activation,<sup>56</sup> and perilla leaf may help with neurological support, according to a rat study—though Nutra-Hist uses **perilla seed**.<sup>57</sup> In another rat study, **lemon balm leaf** extract helped with neurological support.<sup>58</sup>

## Safety and Cautions

**Stinging nettle leaf** (*U. dioica*), **perilla seed** (*P. frutescens*), **lemon balm leaf** (*M. officinalis*), **black cumin seed** (*N. sativa*), **Baikal skullcap root** (*S. baicalensis*), **turmeric root** (*C. longa*), and **noni fruit** (*M. citrifolia*) are generally well-tolerated when used as directed.<sup>59–65</sup> There is insufficient safety evidence for use in pregnancy or breastfeeding.<sup>59–65</sup> Consult a physician before use in bleeding disorders or with blood thinners,<sup>64</sup> with blood sugar medications,<sup>64</sup> or with blood pressure medications.<sup>65</sup> Consult a physician before use with kidney disorders or medications that raise potassium levels, as noni fruit's potassium content may lead to hyperkalemia.<sup>65</sup>

Safety is not documented in breastfeeding or pregnant women, or in children under age 3, due to insufficient safety research.

\*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to treat, cure, or prevent any diseases.

## References

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## NutraMedix

# NUTRA-HIST

**MAST CELL AND HISTAMINE SUPPORT†**

**SHAKE WELL BEFORE EACH USE.**

Put 2 mL in 4 oz. (120mL) of water and wait one minute before drinking, use 2 times a day or as directed by a physician. Do not use if pregnant or nursing. Stop use if adverse reactions develop. Keep out of reach of children. 0.25 mL on calibrated dropper: approx. 5 drops.

**Supplement Facts**

Serving Size: 40 drops (2mL)  
Servings Per Container: 60

Amount Per Serving	% Daily Value
Proprietary Blend	2 mL†
Stinging Nettle leaf extract, Lemon Balm leaf extract, Perilla seed extract, Black Cumin seed extract, Baikal Skullcap root extract, Turmeric root extract, Noni fruit extract	

†Daily Value (DV) not established

Other ingredients: mineral water, ethanol (20-24%)

Lot # 1877209

Exp.

**Dietary Supplement**

**4 fl oz. (120 mL)**

7 28650 06204 8

**NutraMedix**

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[www.nutramedix.com](http://www.nutramedix.com)  
561-745-2917