# Supplementary file

## Composition of herbal immunomodulatory phototherapeutic (IP)

The drops are made out of herbs, spices and of dried fruits (see *Supplementary Table 1*) diluted in 30% alcohol solvent (kindly provided by R. Vendeville, Voorhout, The Netherlands).

**Supplementary Table 1. Composition of IP and IP alcohol-containing solvent**

| Solution | SHC | SHC-solvent |
|---|---|---|
| **Composition** | Blackberry<br>Chamomile<br>Garlic<br>Clove<br>Elderberry<br>Alcohol 30%<br>water | Alcohol 30%,<br>water |

A new immunomodulatory phototherapeutic IP was designed as an anti-inflammatory composition, as its herbal elements were previously shown to reduce the inflammation in clinical and pre-clinical studies (Nunes et al. 2020; Nascimento et al., 2021). For example, garlic is well established as an immunomodulatory and anti-inflammatory agent (Batiha et al., 2020); the consumption of aged garlic extract modulated the distribution of immune cells and prevented an increase in the concentration of TNF and IL-6 in a serum in obese adults (Xu et al., 2018). Lee et al. found that the chloroform extract from aged black garlic reduces TNF–induced NF-κB activation in human umbilical vein endothelial cells (Jeong et al., 2016). Moreover, in the double blind randomized clinical trial the administration of 400 mg of standardized garlic extract resulted in a significant reduction in IL-6, CRP and ESR blood levels (Zare et al., 2019).

The application of vanilla extract was shown to suppress free radical production in a mouse model of cancer (Tai et al., 2011). Elderberry was shown to affect inflammatory markers, although this effect did decline with an ongoing supplementation and it were weaker than that of classic non-steroid ant-inflammatory drugs (Vogl et al., 2013; Wieland et al., 2021). Blackberry was shown to suppress inflammatory response of macrophages (Cenk et al., 2021) and was proposed as a component of medical food with anti-inflammatory properties (Paczkowska-Walendowska et al., 2021).

Extensive literature suggests therapeutic potential of clove, *Syzygium aromaticum*, that is used in traditional medicine to treat inflammation of the mouth and throat, nausea and upset stomach (Han and Parker, 2017). Synergistic interactions between non-steroidal anti-inflammatory drugs and *Matricaria chamomilla* extract were shown to mediate anti-inflammatory effects at the systemic level that might be of therapeutic benefits for the clinical management of inflammatory processes (Ortiz et al., 2017).

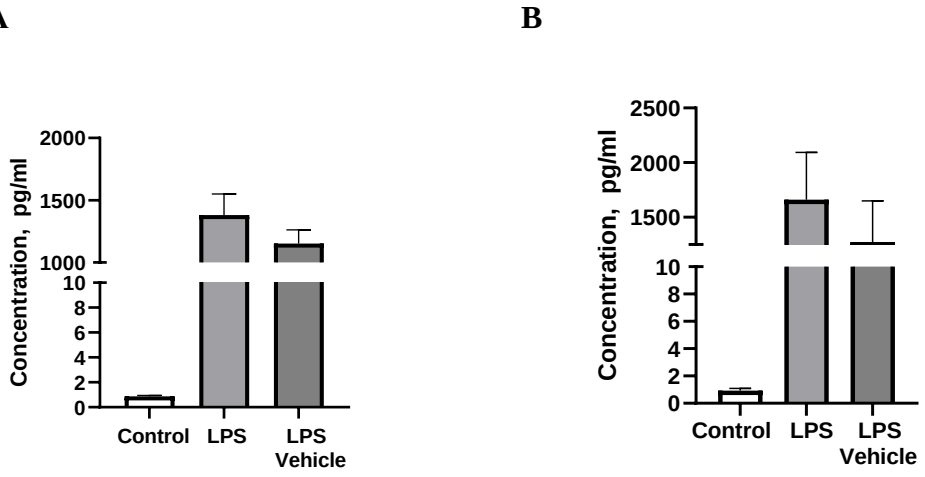
However, many studies suggest that the use of herbal combinations might be more effective in their anti-inflammatory and ant-oxidant action, in comparison with the effects of an individual use of these and other medicinal herbs (Xia et al., 2021).

**LPS-induced cytokine release by human macrophages**

Blood was collected from 42 healthy volunteers and samples of a volume of 9 ml were subjected to a heparinization. Subsequently, the samples were diluted 1:10 with RPMI 1640 medium (ThermoFisher, Gibco, Hennigsdorf, Germany) and were cultured for 6 hours, at the temperature 37º, at 5% CO2, 96%-humidity, with and without LPS (Lipopolysaccharide E. coli, Merck, Darmstadt, Germany) that was used at the concentration of 25 ng/ml. Cell preparations were treated with prednisolone that was applied at its final concentration of 2,5µg/ml, or with IP that was used that the final concentration of a 38% v/v, or remained untreated. Supernatants were collected and concentrations of IL-1β and TNF were determined using flow cytometry according to BD Cytometric Bead Array (CBA). Human Soluble Protein Master Buffer Kit (Becton Dickinson, Franklin Lakes, NJ, USA) was used according the manufacturer instructions.

**Lack of effects of alcohol-containing vehicle on the LPS-induced cytokine release**

Separate pilot studies were carried out to rule out potential effects of the IP-alcohol-containing vehicle on the cytokine release and showed a lack of such effects (*Supplementary Fig.1*). A 30% alcohol-containing vehicle was applied as described above, instead of IP. One-way ANOVA revealed significant group differences in the study with non-stimulated macrophages, LPS-stimulated non-treated macrophages and LPS-stimulated vehicle-treated macrophages in the concentrations of IL-1β and TNF ($F=33.0$, $p<0.0001$ and $F=71.99$, $p<0.0001$, respectively, *Suppl. Fig. 1A,B*). No significant group differences were found between the latter groups in the measured parameters (IL-1β: $p=0.651$, TNF: $p=0.179$, Tukey's test) suggesting that alcohol solution alone does not affect LPS-induced release of the investigated pro-inflammatory cytokines.




**Supplementary Figure 1. Lack of effects of alcohol-containing vehicle on the cytokine release of LPS-stimulated human macrophages. (A)** Concentrations of IL-1β were significantly elevated by LPS application where no group differences were found regardless the use of alcohol-containing vehicle **(B)** Similarly, concentrations of TNF were significantly increased by LPS application, no group differences were found regardless the use of alcohol-containing vehicle. Data presented as mean ±SEM.

**Administration of resiquimod**

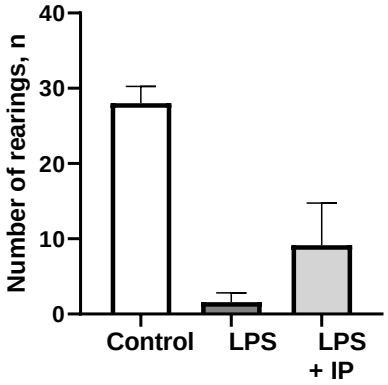
Stock R848 (resiquimod, see the main text) was prepared by diluting in DMSO to a concentration of 10mg/mL. Stock resiquimod was then diluted 1:10 in sterile saline to 1mg/mL

and 200µL of the working solution was injected intraperitoneally (200µg of resiquimod per mouse). Control animals received sterile saline. All animals were culled 6 hours post-challenge.

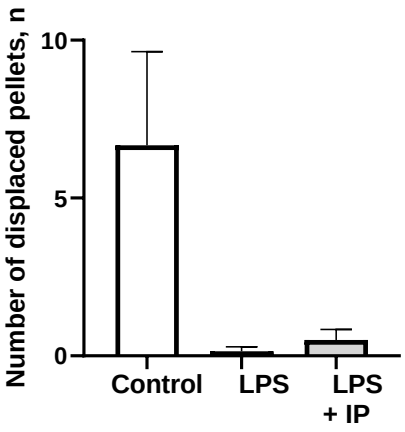
**'Ceiling' behavioral changes in mice challenged with 0.1 mg/kg of LPS**

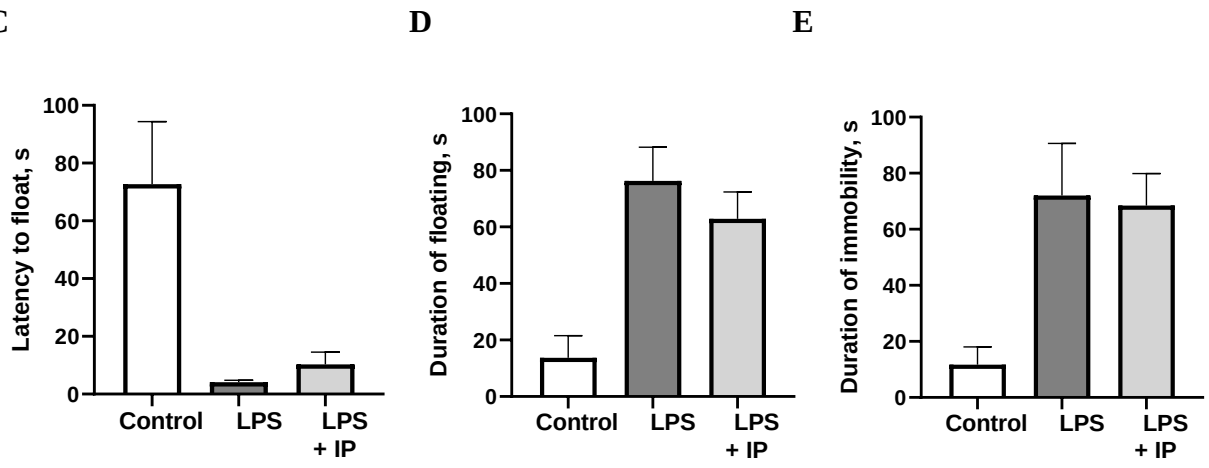
I order to determine an optimal dose of LPS injection in a mouse model of 'sickness behavior', a separate study was carried out using the novel cage test, marble test, forced swim model and the tail suspension paradigm. These experiments have shown 'ceiling' behavioral changes in mice injected with the dose of LPS of 0.1 mg/kg and studied 6 h thereafter (*Supplementary Fig.2*). There were significant group differences in the number of rearings in the novel cage ($F=17.23$, $p<0.0001$, one-way ANOVA), and, in comparison to non-challenged mice, significant decrease in this parameter in the LPS-non-treated mice ($p<0.0001$) and in IP-treated LPS-challenged animals $p=0.0019$, Tukey's test, *Suppl. Fig.2A*). As for the number displaced pellets in the marble test (Veniaminova et al., 2021), significant group differences were found ($F=4.93$, $p=0.029$). In comparison to non-challenged mice, there was a significant decrease in this parameter in the LPS-non-treated mice ($p=0.0291$) and IP-treated LPS-challenged animals $P=0.048$, *Suppl. Fig.2B*). In the forced swim test, there was a significant group difference between the groups in the latency to float ($F=10.34$, $p=0.0012$). In comparison to non-challenged animals, the latency to float was significantly shorter in the LPS-non-treated mice ($p=0.0018$) and IP-treated LPS-challenged animals $P=0.004$, *Suppl. Fig.2C*). In this model, there was a significant group difference between the groups in the duration of floating ($F=10.05$, $p=0.0013$). In comparison to the non-challenged group, the duration of floating was significantly longer in the LPS-non-treated mice ($p=0.0013$) and IP-treated LPS-challenged animals $P=0.0094$, *Suppl. Fig.2D*). In the tail suspension paradigm, there were significant group differences in the duration of immobility ($F=8.35$, $p=0.0039$). In comparison to the non-challenged group, the duration of immobility was significantly longer in the LPS-non-treated mice ($p=0.012$) and IP-treated LPS-challenged animals $p=0.0067$, *Suppl. Fig.2E*).

**A**




**B**






**Supplementary Figure 2. The dose of LPS of 0.1 mg/kg has induced profound behavioural changes. (A)** In the novel cage test, significant decrease in the number of rearings was found in the LPS-non-treated and IP-treated LPS-challenged mice in comparison with non-challenged controls. **(B)** In the marble test, the number of displaced pellets at 30$^{th}$ min of the test was significantly smaller in the LPS-non-treated and IP-treated LPS-challenged mice in comparison with non-challenged mice. In the forced swim test, in comparison to non-challenged animals there was a significant **(C)** decrease in the latency to float and **(D)** an increase in the duration of floating in both LPS-injected groups. **(E)** Similarly, the duration of immobility was significantly longer in the LPS-non-treated mice and IP-treated LPS-challenged animals than in the non-challenged group. Data presented as mean ±SEM.

## Behavioural testing

Behavioural tests were carried out during the active period of the animals' light cycle (between 09:00–17:00); behaviour was recorded and scored offline. The experimenter was unaware of treatment each animal had received. Behavioural equipment was thoroughly cleaned with water between each test.

*Novel Cage*

The 5-min long novel cage test was carried out to assess exploration of a new environment as described elsewhere (Strekalova et al., 2004, 2015, Couch et al., 2016). Mice were introduced into a standard plastic cage (21 cm x 21 cm x 15 cm) filled with fresh sawdust. The number of exploratory rears was counted under red light per each minute, and summed up for minutes 1-5 of the test.

*Open Field*

In the open field model, mice were placed in a square white plastic box (45 x 45 x 45 cm) illuminated with white light (25 lx) near the wall for 10 min (Open Science, Moscow, Russia). The number of crossings of peripheral zone of the arena (0-10 cm from the wall) and remaining central area, a measure of anxiety-like behaviour were scored as described elsewhere (Pavlov et al., 2019; de Munter et al., 2021). The recordings were analysed using the automated video-tracking Viewpoint software (Viewpoint, Lyon, France).

*Forced swim test*

The test was carried out as described elsewhere (Malatynska et al., 2012). Animals were placed into a plastic transparent cylinder (Ø 17 cm) filled with water (+23°C, water height 13 cm, cylinder height 20 cm) under subtle lightning (light intensity 25 lx) for 6 min. Their parameters of floating behaviour that was defined by the absence of any directed movements of the animals' head and body. The total time spent floating was evaluated for the entire duration of the test, the latency to float was recorded as well using the automated video-tracking Viewpoint software (Viewpoint, Lyon, France).

**Supplementary Table 2. Sequences of primers used for qRT-PCR**

Primers were purchased from Sigma. Relative expression was determined by the 2-ΔΔCT method, normalized to GAPDH as the housekeeping gene (PrimerDesign).

| Gene | Forward primer 5′–3′ | Reverse primer 5′–3′ |
|---|---|---|
| GAPDH | TGCACCACCAACTGCTTAG | GGATGCAGGGATGATGTTC |
| SAA-2 | TGGCTGGAAAGATGGAGACAA | AAAGCTCTCTCTTGCATCACTG |
| ACE-2 | GGGTGGTGCTGAAGTACGAT | CCAAAGACTGCTTTGCATCA |
| CXCL1 | GCTGGGATTCACCTCAAGAAC | TGTGGCTATGACTTCGGTTTG |
| CXCL10 | CATCCCGAGCCAACCTTCC | CACTCAGACCCAGCAGGAT |
| IL-1β | TGTAATGAAAGACGGCACACC | TCTTCTTTGGGTATTGCTTGG |
| IL-6 | ACTCACCTCTTCAGAACGAATTG | CCATCTTTGGAAGGTTCAGGTTG |

**High-potency-liquid chromatography (HPLC)-high-resolution-mass-spectrometry (HRMS)**

The analysis of herbal IP was carried out by the means of HPLC method followed by tandem mass spectrometry of high resolution (HPLC/MSHR). For the assay, an aliquot of 0.2 mL was placed to a centrifuge tube of 2.0 mL and 1.0 mL of ethanol was added. After shaking for 5 min, this mixture was centrifuged at the speed 10 000 / min for 5 min. Next, the solution was analyzed using the chromatographic system Agilent 1290 Infinity II (Agilent Technologies, Santa Clara, CA, USA), in conjunction with quadrupole-time streaming high precision mass detector Agilent 6545 Q-TOF LC/MS (Agilent Technologies, Santa Clara, CA, USA).

Chromatographic segregation was carried out using the column Zorbax Eclipse Plus C18 RRHD 2.1 mm × 50 mm × 1.8 μm (959757-902, Agilent Technologies, Santa Clara, CA, USA) and a 5 mm-pre-column (821725-901, Agilent Technologies, Santa Clara, CA, USA) under thermostat temperature of 35C°. For the fluent component phase, a 0.1% water solution of formic acid was used (solvent A) as well as an acetonitrile solution (solvent B). The speed of flow was 0.4 mL/min. The analysis was undertaken in a gradient regimen, a content of a solvent B was determined to be linear in a range from 5 to 100% till the 15$^{th}$ minute, the solution was kept under 100% B content till the 17$^{th}$ min, followed by a switch to a 5%-solvent B; a stabilization of

a fluent component was performed for another 2 min. The volume of the sample introduced was 1 μL.

The quadrupole-time streaming high precision mass detector was applied along with the source of ionization using electro spreading elements (Dual AJS ESI) under the conditions of ionization of positively and negatively charged ions. N2 was employed for a drying gas, under a temperature of 350C$^{o}$ and the speed of a flow of 10 L/min. The temperature of additional overheating gas was 400 $^{o}$C and the speed of a flow was 12 L/min, 90W fragmentation power. Under the conditions of mass spectrometry (MC), the quadrupole was tuned for streaming a full ion current, under conditions MC$^2$, the quadrupole has released only ion-precursor as a proteinized molecule of reference in a spectrum Δm/z=1.3 a.m. Dissociation spectra that were induced by strikes (DIS) that were measured under MC$^2$ conditions were obtained as a result of strikes of ion-precursor molecules against N2 molecules with energy calculated in a range: 10 - 50 eW. A range of scanning of mass was 100–1700 Da in MC regime and 30–700 Da in the MC$^2$ regime. The detector was functioning under conditions of enlarged dynamic range (EDR) of 2GHz, the speed of scanning was 1.5 spectra / sec. The tuning of the device and adjustment of the bore for a precision of mas definition was carried out automatically in real time using standard calibrating solutions, according to manufacturer instructions.

The identification of the components of investigated composition was carried out by the determination of exact mass and calculations of brutto-formula of the components, as well as by the use of previously obtained in a course of MC2 experiments DIS spectra and a comparison of these data against available standard data banks (NIST 17 MS /MS, Metlin AM PCD, MoNA MassBank GNPS).

**Supplementary Table 3. Summary of mean and SEM for gene expression in liver**

The analysis of relative fold expression of mRNA of immunomodulatory factors in the liver of mice with induced systemic inflammation has revealed the effects of inflammatory challenge and herbal IP (*Supplementary Table 3*; see also the main text and Fig.2).

| **Groups** | **Genes** | | | | | |
|---|---|---|---|---|---|---|
| | **SAA-2** | **ACE-2** | **CXCL 1** | **CXCL 10** | **IL-1B** | **IL-6** |
| **Control** | 1.0±0.32 | 1.0±0.23 | 1.0±0.23 | 1.0±0.12 | 1.0±0.08 | 1.0±0.19 |
| **Resiquimod** | 366.93±12.76 | 0.94±0.11 | 28.70±5.41 | 210.07±40,89 | 4.84±0.59 | 5.03±0.84 |
| **IP** | 1.96±0.74 | 0.92±0.06 | 2.25±1.39 | 1.21±0.42 | 1.19±0.12 | 1.04±0.14 |
| **Resiquimod + IP** | 348.04±22.59 | 0.64±0.07 | 23.16±3.29 | 114.25±16.80 | 4.44±0.30 | 4.53±0.71 |

A comparison of relative fold expression of mRNA of immunomodulatory factors in the spleen of mice with induced systemic inflammation has revealed the effects of inflammatory challenge and herbal IP (*Supplementary Table 4*; see also the main text and Fig.2).

**Supplementary Table 4. Summary of mean and SEM for gene expression in spleen**

| Groups | Genes | | | | | |
|---|---|---|---|---|---|---|
| | **SAA-2** | **ACE-2** | **CXCL 1** | **CXCL 10** | **IL-1B** | **IL-6** |
| **Control** | 1.0±0.6 | 1.0±0.3 | 1.0±0.04 | 1.0±0.04 | 1.0±0.26 | 1.0±0.014 |
| **Resiquimod** | 9.52±3.78 | 2.27±1.25 | 8.16±4.62 | 5.9±2.18 | 3.87±1.92 | 1.43±0.23 |
| **IP** | 82.60±5.77 | 2.19±0.32 | 0.94±0.03 | 0.88±0.02 | 0.97±0.1 | 1.0±0.02 |
| **Resiquimod + IP** | 143.39±8.63 | 235±0.24 | 2.01±0.43 | 5.53±1.04 | 2.44±0.48 | 1.10±0.04 |

Blood cell counts of mice with induced systemic inflammation were affected by inflammatory challenge and herbal IP (*Supplementary Table 5;* see also the main text and Fig.3).

**Supplementary Table 5. Summary of mean and SEM for absolute data on the number of blood cells**

| Groups | Blood cells | | | | |
|---|---|---|---|---|---|
| | **Neutrophils** | **Monocytes** | **Eosinophils** | **Lymphocytes** | **Basophils** |
| **Control** | 1.09±0.15 | 0.18±0.05 | 0.6±0.18 | 1.3±0.18 | 0.08±0.02 |
| **Resiquimod** | 1.32±0.47 | 0.13±0.05 | 3.15±1.87 | 1.23±0.36 | 0.68±0.62 |
| **IP** | 1.78±0.25 | 0.19±0.08 | 1.31±1.44 | 1.14±0.2 | 0.05±0.01 |
| **Resiquimod + IP** | 0.47±0.10 | 0.05±0.01 | 2.28±0.55 | 0.87±0.15 | 0.06±0.01 |

**HPLC-HRMS analysis of herbal IP and its physiological properties**

Based on the methodology applied, the detection of negatively charged ions did not reveal any compounds. For mass-spectrochromogramm that was recorded for positively charged ions, the threshold of detection was set up as 50000 counts. 11 compounds were identified as constituents of herbal IP (*Supplementary Table 6*).

**Supplementary Table 6**. **Chemical composition of IP: the main constituents**

| N | Retention time, min | $[M+H]^+$, measured | Name of compound | Brutto-formula | Relative content, % |
|---|---|---|---|---|---|
| 1 | 0.40 | 104.1075 | Choline | $C_5H_{13}NO$ | 11.5 |

| | | | | | |
|---|---|---|---|---|---|
| 2 | 0.87 | 132.1022 | Isoleucine | $C_6H_{13}NO_2$ | 1.38 |
| 3 | 0.95 | 294.1549 | *N*-Fructosyl or glucosyl isoleucine (leucine) | $C_{12}H_{23}NO_7$ | 4.47 |
| 4 | 1.42 | 166.0863 | Phenylalanine | $C_9H_{11}NO_2$ | 1.75 |
| 5 | 2.16 | 291.1015 | γ-Glutamyl-(S)-allyl-cysteine | $C_{11}H_{18}N_2O_5S$ | 4.68 |
| 6 | 2.27 | 205.0970 | Tryptophan | $C_{11}H_{12}N_2O_2$ | 0.37 |
| 7 | 3.12 | 295.1293 | Glu-Phe | $C_{14}H_{18}N_2O_5$ | 2.73 |
| 8 | 3.16 | 355.1022 | Chlorogenic acid | $C_{16}H_{18}O_9$ | 2.17 |
| 9 | 3.42 | 395.1311 | Syringin | $C_{15}H_{18}N_6O_7$ | 0.8 |
| 10 | 5.93 | 465.1022 | Isoquercitin or Hyperoside | $C_{21}H_{20}O_{12}$ | 0.35 |
| 11 | 6.04 | 465.1020 | Isoquercitin or Hyperoside | $C_{21}H_{20}O_{12}$ | 0.4 |

**Reported physiological effects of the main constituents of IP**

Utilizing World of Science (WoS) search engine, we conducted a comprehensive search of articles focusing on biological functions and, specifically, role in immunomodulation of herbal IP compounds. We used WoS search engine to find articles featuring search terms "biological role", "immunomodulation" or "inflammation" and a name of a chemical compound to identify these studies. We limited record types to journal articles and reviews, eliminating conference proceedings. The criteria set for the literature search covered the last 40 years of publication period. The results of this search summarizing the main physiological and immunomodulatory properties of IP constituents and key representative references are presented in a *Supplementary Table 7*.

**Supplementary Table 7. Functions of IP chemical ingredients in the physiology and immunomodulation**

| Name of compound | Functions in physiology | Functions in immunomodulation |
|---|---|---|
| Choline | Key role in the synthesis of phospholipid components of cell membranes, and in the synthesis of plasma lipoproteins. It plays crucial role in acetylcholine synthesis (Hollenbeck, 2012), expression of the molecules regulating synaptic plasticity: G9a, Prmt1, Ahcy, Dnmt1, Mat2a (Blusztajn and Mellott, 2012; Craciunescu et al., 2003), exerts pro-proliferative effects in the dentate gyrus (Wong-Goodrich et al., 2008) potentially via the up-regulation of hippocampal expression of Insulin-like growth factor 2 (IGF2) (Cline et al., | Anti-inflammatory and anti-oxidative stress effects in patients with asthma (Mehta et al., 2010). Higher choline levels were associated with protective effects on the fetal brain in humans (Chowdhurya, Pathakwhich, 2020) and promoted maturation, improved immune responses of the offspring in a rat (Lewis et al., 2016). |

| | | |
|---|---|---|
| | 2012, 2015). | |
| Isoleucine | Regulates glucose consumption and utilization via acting on the intestinal and muscular glucose transporters (Zhang et al., 2017), increases insulin receptor sensitivity and the browning of white adipose tissue (Ma et al., 2020); regenerative effects in the skin injury model, a counteraction of nitrosative stress (Nie et al., 2018), a suppression of $H_2O_2$-mediated oxidative stress (Katayama et al., 2007). | Induction of the expression of peptides regulating host innate and adaptive immunity (Gu et al., 2019), ameliorative effects on the parameters of oxidative stress: a decrease of malondialdehyde concentration, protein carbonyl content, and an increase of the activities of anti-oxidant defense enzymes: superoxide dismutase, catalase, and glutathione reductase (Zhao et al., 2014), a stimulation of the immune response via β-defensin (Mao et al., 2013). |
| *N*-Fructosyl or glucosyl isoleucine (leucine) | The pivotal regulator of protein folding, oligomerization and transport (Helenius and Aebi, 2000), the regulator of protein metabolism that counteracts protein degradation (Nair et al., 1992) and stimulates muscle protein synthesis, enhancement of insulin-receptor signaling in a muscle (Garlick et al., 2005), a promotion of somatic growth (Zhou et al., 2020), anti-stress effects (Koo and Howe, 2012). | An anti-inflammatory action under hyper-catabolic conditions that is mediated via the L-glutamine pathway (Cruzat et al., 2014), antioxidant and immune-regulating effects (Zhou et al., 2020). |
| Phenylalanine | Crucial role in the synthesis of proteins, catecholamines and melanin (DePietro, Fernstrom, 1999) due to its function of a precursor of the amino acid L-tyrosine Phenylethylamine that regulates lipid metabolism, increases extracellular levels of dopamine, modulates noradrenergic transmission and antagonizes GABA(B) receptor-mediated signaling, suppressing their inhibitory effects (Perkowski, Warpeha, 2019). | A regulation of immune response to viral infection, as shown in IFN-α – treated HCV patients (Murr et al., 2014) and implication in altered neuro-immune abnormalities and inflammatory responses in the patients with various neuropsychiatric disorders including major depressive disorder (Strasser et al., 2017); anti-inflammatory effects that are mediated via a suppression of the accumulation of lipids in the liver (Byun et al., 2017), a suppression of ROS (Chen et al., 2016; Oliva et al., 2020). |
| γ-Glutamyl-(S)-allyl-cysteine | Anti-oxidative stress effects during aging and under various pathological conditions that are associated with compromised free radical cellular scavenging (Colín-González et al., 2012), metal-chelating properties, inhibition the synthesis of glycation end products (AGEs) (Tan et al., 2015). | Stimulation of scavenging of free radicals and pro-oxidant species, induction of the antioxidant enzymes and Nrf2 factor, inhibition of pro-oxidant enzymes (Colín-González et al., 2012); an inhibition of the main protease of SARS-CoV-2 (Parashar et al., 2021). |
| Tryptophan | A precursor of serotonin, and thus, key roles in numerous physiological processes such as the sleep-wake cycle, appetite, mood, gut functions, and pain (Richard et al., 2009; Carneiro et al., 2018; Yamamoto et al., 2021). | Anti-inflammatory and anti-oxidative actions that is mediated via calcium-sensing receptor activation (Kim et al., 2010; Xu et al., 2017). A regulation of T-cell proliferation and anti-inflammatory effects via serotonin, a suppression of immune cells via downstream metabolites and pro-apoptotic mechanisms (Widner et al., 2000; Moffett, Namboodiri, 2003). |
| Glu-Phe | A suppression of the lipogenesis in | A suppression of the immune response to an |

| | | |
|---|---|---|
| | hepatocytes and a regulation of hepatic lipid homeostasis (Lee et al., 2017). | immunization in mice (Babu, Maurer, 1984). |
| Chlorogenic acid | Pivotal roles in glucose and lipid metabolism and beneficial anti-diabetic, anti-carcinogenic, anti-inflammatory, antimicrobial, anti-obesity and mnemotropic effects (Tajik et al., 2017; Kumar et al., 2020), neuroprotective and anti-ischemic effects (Sato et al., 2011; Yun et al., 2012; Feng et al., 2016; Lee et al., 2020). | Powerful effects on the innate immunity through MDA5, TLR7 and NF-κB signaling pathways (Abaidullah et al., 2021), also via vascular modulation chemotaxis, macrophage activation, cytokine secretion, and immunoglobulin production (Bagdas et al., 2020), a suppression of a generation of pro-oxidant and pro-inflammatory factors SOD-2, IL-2, TNF, activation of antioxidant enzymes and anti-inflammatory cytokines: IL-4, IL-13 (Lee et al., 2020) |
| Syringin | The inhibition of adipocyte differentiation, adipogenesis, stimulation of lipid metabolism (Hossin et al., 2021) and of muscle glucose uptake and utilization in muscles, anti-diabetic effects (Niu et al., 2008). | Anti-inflammatory and neuroprotective properties via anti-FOXO3a /NF-κB activities (Tan et al., 2021), anti-allergic effect that is mediated by an in inhibition of TNF and IL-1β production and cytotoxic T cell proliferation (Cho et al., 2021; Song et al., 2010). |
| Isoquercitin | A stimulation of scavenging of reactive oxygen species (Hammer et al., 2007; Li et al., 2020) resulting in a reduced depletion of glutathione and an attenuation of the nitric oxide-induced lipid peroxidation (Jung et al., 2010); an anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, and psychostimulant activities, anti-coagulation action, regulation of capillary permeability and stimulation of mitochondrial biogenesis (Li et al., 2016). | Antioxidant and anti-inflammatory effects that are mediated through direct scavenging of reactive oxygen/nitrogen species (ROS/RNS) and the Inhibition of prooxidant enzymes, prostaglandins and, cytokines production, an induction of antioxidant enzymes (Hammer et al., 2007; Valentová et al., 2014; Procházková et al., 2011; Kim et al., 2014). Beneficial immunomodulatory effects in patients suffering from rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and systemic lupus erythematosus in humans or animal models that are mediated via the induction of Th-1 derived cytokine, IFN-γ and inhibition of Th-2 derived cytokine, IL-4 (Nair et al., 2002; Shen et al., 2021). |
| Hyperoside | Antioxidant, anti-hyperglycemic, anti-cancer, anti-inflammatory, and anticoagulant activities (Yang et al., 2021); anti-atherosclerosis and anti-stress mnemotropic effects (Gong et al., 2017). | Anti-inflammatory effects that are mediated by NLRP1-pathway (Ku et al., 2014), the NF-κB signaling mechanisms (Jin et al., 2016) and other LPS-induced inflammatory responses. |

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