Healthy Strong

scientifically-based concepts and ideas for formulating products with M.E.D. Propolis

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This document is exclusively intended to inform operators in the pharmaceutical and nutraceutical sector.
The information therein contained are not intended to give consumers any specific health advice.

B NATURAL
PROPOLIS AND BEEKEEPING DERIVATIVES

Propolis: the beehive's immunitary system

Since ancient times food supplements have been used to improve the health and the wellness, but today of all days it is crucial to stay healthy and strong!

The watchword is "equilibrium" to be ready, reinforcing the immune system and protecting the mucosae.

Our research has always been oriented to protect the upper respiratory tract and improve the immune system. Here we want to underline some strategies in which the characterized polyphenol complex from M.E.D. Propolis can be used to help the body.

The **holistic approach to protect the body** could be, academically, divided in tree steps:

Avoid the entrance of the microorganisms

Modulate the immune system

Regulate the local and systemic anti-inflammatory response

Since **Propolis is a natural source of polyphenols**, containing more than 50% and more than 300 different polyphenols, it is one of the most interesting product able to reach these goals. In nature there is **no vegetable source with the same etherogeneity and richness of polyphenols as Propolis**, since it can count on the hard work of the bees that collect and mix the best polyphenols of different plants.

In literature, there are hundreds of studies supporting the healthy properties of propolis, such as, immunomodulatory, wound healing, gastroprotective, hepatoprotective and antidiabetic activities. These propolis properties are ascribed to three **main activities namely antioxidant, anti-inflammatory and antimicrobial**.

Propolis is a resinous matrix that bees (*Apis mellifera*) collect from gems, exudates and plants, resulting in a heterogeneous mixture of many substances harvested, processed and used by bees to close hive holes and to protect it: Propolis functions as the immune system of the beehive. Despite bees live in an environment having high humidity rate and a temperature of 37°C, thanks to propolis they keep out bacteria, molds and fungi.

The development of technological and analytical techniques, grounded on a long history in propolis extraction, has lead B Natural to the production of high quality, patented propolis extracts (**M.E.D. Propolis**), with standardized and characterized polyphenolic complex.

M.E.D. Propolis - that assures same activity in every extract and batch - is supported by *in vitro* and *in vivo* evaluations as well as clinical trials to prove the healthy effects.

Avoid the entrance of the microorganisms: *the invisible mask*

When a pathogen breaches the initial barriers of the skin or a mucosal surface, both soluble and cellular innate defences mechanisms are encountered and an inflammatory response is rapidly initiated. Some of the most potent soluble antimicrobial factors encountered include complement, lysozymes, defensins, mucins, lectins, cathelicidins and lipocalins (Chairatana et al., 2017).

In the upper respiratory tract, mucous membranes covered with secreted mucous, provide an innate barrier to infections. Reinforcing this barrier may be a good treatment strategy. For instance, barrier could be strengthened by applying a formulated solution in form of mouth spray or an orosoluble tablet.

As regard the spray, the barrier consists of glycerol, alcohol and M.E.D. Propolis extract. In the formulation, the **combination of glycerol and M.E.D. Propolis exerts a barrier function when applied to the pharyngeal mucous membrane.** Glycerol, a natural humectant, attracts and retains nearby liquid and virus particles via absorption due to its high osmotic activity (Rowel et al.,2009), while Propolis partly degrades protein structures presented on the viral capsid, and thereby reduces the potential interaction between viral capsids and epithelial cells, resulting in a decreased viral load (Tewtrakul and Suhadhirasakul, 2003). The viral load is of importance as there is a dose-response function between exposed virus dose and probability of getting infected (Wilson et al., 2008).

A particularly important application is in the treatment of diseases of the oral cavity. It is also effective in fighting viruses (Šabanović et al., 2019). Moreover M.E.D. Propolis improves the healthy of epithelium and mucosa through its anti inflammatory, antioxidant and antibacterial activity as demonstrated in *in vitro* and clinical studies (Zaccaria et al., 2017, 2019, Esposito et al.2020).

Modulate the immune system: *the bodyguard*

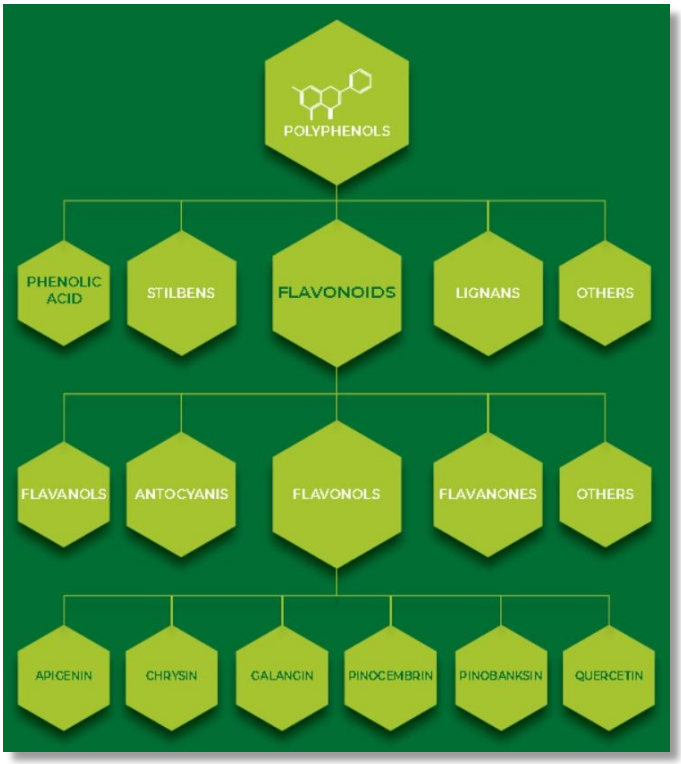
Immune response is one of the most complex mechanisms of the living body, involving the strong cooperation of a large variety of cell types for defending against any potential dangerous agent and even against the occurrence of chronic diseases, making **the regulation of the immune system a key factor in maintaining a healthy equilibrium of the body**.

Modulation of immune system is a challenge, due to complex mechanisms involved and to route of administration. Immune dysfunction is caused by various factors, including changes in relevant immune regulators and environmental stress. Immune system imbalance leads to a variety of diseases in humans. Nutrition may play an essential role in immunity by interfering with proinflammatory cytokine synthesis, immune cell regulation, and gene expression.

Polyphenols exhibit a range of biological activities promoting immunity to foreign pathogens via various pathways. Different immune cells express multiple types of polyphenol receptors that recognise and allow cellular uptake of polyphenols, which subsequently activate signalling pathways to initiate immune responses. Polyphenols are well-known, active compounds with immunomodulatory activity (Szliszka et al., 2011). Furthermore, the polyphenols can induce epigenetic changes in cells. In summary, polyphenols can be used to regulate intestinal mucosal immune responses, allergic diseases, and immunity.

Accordingly, functional foods, defined as those providing specific nutrition or targeting multiple functional components, are considered a form of preventive medicine (Cornò et a., 2016). Dietary **interventions that involve polyphenols may modulate immune responses** by affecting epigenetic mechanisms, such as regulatory DNA methylation, histone modification, and microRNA-mediated post transcriptional repression that alter the expression of genes encoding key immune factors. Immune cells express many receptors that allow the transmission of external stimuli to activation processes within the cell *in vivo*. In particular, M.E.D. Propolis it is absorbed *in vivo* (Curti et al., 2019) and it works with epigenetic mechanism of action (Zaccaria et al., 2017).

More than 300 polyphenols have been isolated in propolis samples. The extract obtained with the patented Multi Dynamic Extraction method contains the integral complex of polyphenols naturally present in propolis, it is pure from inactive resins and it is rich in polyphenols. In particular, obtained propolis extract called M.E.D. Propolis, is characterized and standardized by the presence of a biologically active polyphenol complex, identified in six major polyphenols: **galangin, chrysin, pinocembrin, apigenin, pinobanksin, quercetin,** having a relative concentration in the extract always greater than 25% (w/w) determined in HPLC-ESI-MS. Due to the natural complexity of propolis raw materials, in order to assure and guarantee the constant quantity and quality of active compounds, in all M.E.D. Propolis extracts the total polyphenols and the characterized polyphenols complex are determined and quantified by HPLC-ESI-MS (Volpi & Bergonzini, 2006).



Several studies have been conducted to determine the role of polyphenols in the modulation of immune system acting on innate and adaptative response. Intake of representative polyphenols can improve a skewed Th1/Th2 balance and suppress antigen-specific IgE antibody formation (Kumazawa et al., 2014). This was suggested as one mechanism of action of **quercetin** contributing to its anti-inflammatory and immunomodulating properties having potential of being utilized in several types of allergic reactions. **Quercetin** is able to inhibit IL-6 and IL-8 better than cromolyn (antiallergic drug

disodium cromoglycate) (Mlcek et al., 2016). In allergic diseases, besides the influence on Th2 activation, regulatory T cells represent another possible target for polyphenols activity (Magrone et al., 2008). **Apigenin** contain hydroxyl groups in their backbone, and it was suggested that these might be involved in immunomodulatory activities. **Chrysin, quercetin, and galangin** increase IL-2 secretion, while EGC, **apigenin**, and fisetin inhibit the secretion by IL-2R alpha-dependent mechanism (Yu et al., 2008). There was no obvious structure-activity relationship with regard to the chemical composition of the flavonoids and their cell biological effects (Lyu et al., 2005). IL-2 receptors play a central role in lymphocyte proliferation and immune reactivity (Cox et al., 1987,1988). IL-12 is the most important factor driving Th 1 immune responses. **Quercetin** blocks IL-12-dependent JAK-STAT signalling in Th cells (Yu et al., 2008), **chrysin** (Xiao et al., 2014) shows the strongest inhibitory effect on IL-12 production. **Apigenin** and **chrysin** have inhibitory effect on IL-1b secretion (Zhang et al.,2014) in splenic mononuclear cells (Xiao et al., 2014); **quercetin** (Mlcek et al., 2016), 6-gingerol (Kawamoto et al., 2016), and **ellagic acid** (Allam et al., 2016) suppress interleukin IL-4 production, one of the key cytokines secreted by Th2 cells.

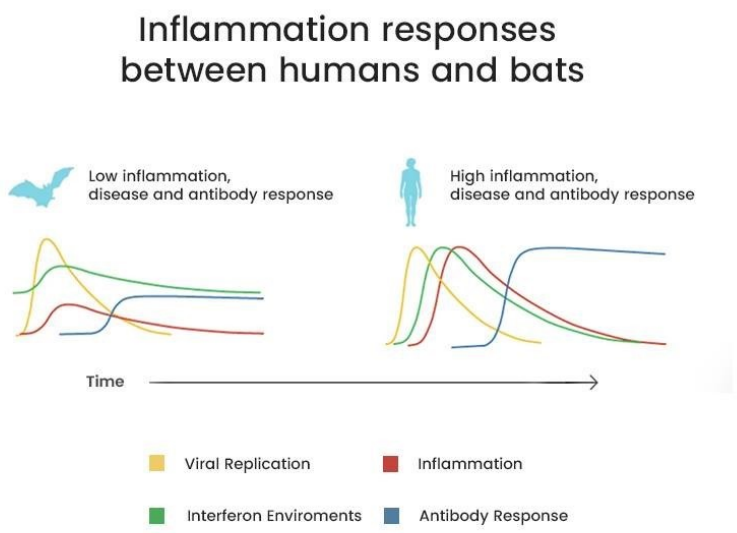
Suppression of LPS-induced expression of pro-inflammatory cytokine IL-6 is induced by flavonoids (Liu et al., 2014), **quercetin** attenuates TLR7-induced expression, effect of mediated by HO-1 (Yasui et al., 2015), **chrysin** (Xiao et al., 2014), **apigenin**, through modulating multiple intracellular signaling pathways in macrophages and prevents LPS-induced IL-6 production by reducing the mRNA stability via inhibiting ERK1/2 activation (Zhang et al.,2014). Based on the inhibitory effect on TNF-α secreted by LPS-stimulated cells, flavonoids were classified in four groups: strong (flavones, flavonols, chalcones), moderate (flavanones, naringenin, antocyanidin, pelargonidin), weak (genistein), and inactive (eriodictyol) (Kumazawa et al., 2006). Several phenolic phytocompounds successfully suppress the expression of pro-inflammatory cytokines such as TNF-α: **quercetin** (Yasui et al., 2015), **ellagic acid** (Allam et al., 2016), **apigenin** (Zhang et al.,2014), **chrysin** (Xiao et al., 2014).

Chrysin inhibited the splenic mononuclear cell secretion of IFNγ, **quercetin** (Yu et al., 2008), ellagic acid (Allam et al., 2016), syringic and vanillic acid (Itoh et al., 2009), equol (4′,7-isoflavandiol) (Guo et al., 2007) are suggested to exert T-bet-dependent IFNγ suppression.

Nuclear factor κB (NF-κB) plays an important role in inflammatory processes, in autoimmune response, apoptosis, and cell proliferation, by regulating the genes involved in these processes. This factor is activated mainly under conditions of oxidative stress, under the action of various pathogenic stimuli (viruses and bacteria but also inflammatory cytokines). Because of its effects on vital biological processes, modulation of its activation pathway is of great therapeutic potential. In LPS stimulated macrophages, activation of NF-κB that is inhibited was reported for caffeic acid phenethyl ester (**CAPE**) (Jung et al., 2008), **astragalin** (kaempferol-3-O-glucoside) (Kim et al., 2011), naringin (Manna et al., 2015), **quercetin** (Qureshi et al., 2011), and **apigenin** (Yoon et al., 2006). The main mechanism of inhibition consists in the degradation of inhibitor κB and nuclear translocation of NF-κB p65 subunit. These events are strongly linked with modulation of reactive oxygen species generation. Dietary flavonoid naringin induces regulatory T cells through AhR-mediated pathways (Wang et al., 2012). These receptors appear to be involved in various types of toxicity (Tomaszewski et al., 2008, Terao et al., 2011).

Regulate the local and systemic anti-inflammatory response

Many severe virus and bacterial infections are related to excessive inflammation-associated pathology in humans (Gu et al., 2007, Lau et al., 2013). Regulation of such inflammatory responses is crucial in order to limit tissue damage. Strong and chronic inflammation has been associated with poor disease prognosis and health issues in humans and other susceptible animal models (Bradley 2008, De Diego et al., 2014).



readapted from David T. S. Hayman 2019

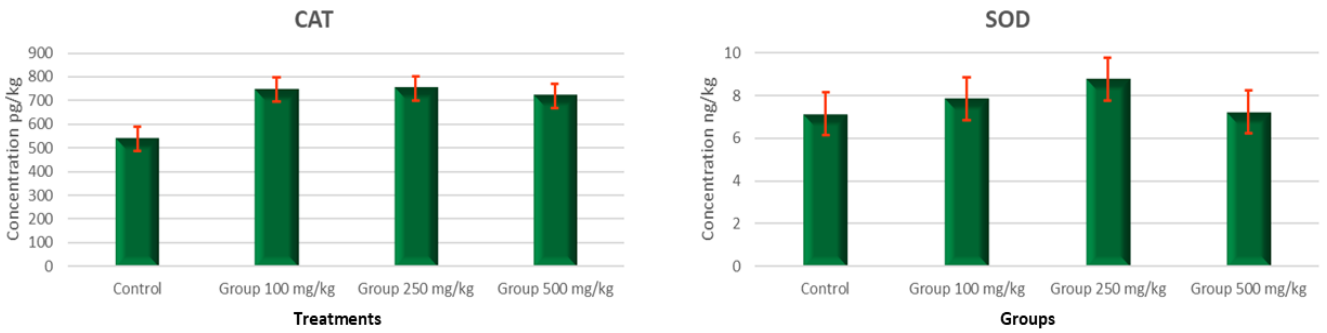
In nature, bat is one of the most relevant viral reservoir: these animals contain hundreds of different viruses including Coronavirus, Hantavirus, Ebola. **Bats seem to tolerate infections because its immune system does not overreact**. A bat's ability to contain the inflammatory response is believed to be one of the reasons they are able to harbour many types of viruses. Bats have evolved novel mechanisms to limit virus-induced proinflammatory responses, while maintaining type I IFN responses to limit virus propagation. Understanding how bats limit virus-induced pro-inflammatory processes may enable researchers to adapt these strategies to counteract inflammation in humans. The ability of bats to control high levels of inflammation may also explain their long life span (Foley et al.,2014, Kacprzyk et al.,2017) in addition to their ability to host (Bray, 2014) multiple viruses in the absence of clinical disease (Haymann, 2019).

A recent study found that the magnitude of the inflammatory cytokine response detected following stimulation of monocytes with different pathogen-derived products, including those from influenza A virus, differs in different seasons. In the individuals studied, inflammatory cytokine responses were maximal during the summer months of June and July and weakest in winter months (Horst et al., 2016).

Other virus infections lead to acute respiratory distress syndrome (ARDS) that is a clinical syndrome of non-cardiogenic pulmonary oedema associated with bilateral pulmonary infiltrates, stiff lungs and refractory hypoxaemia. ARDS is characterized by an explosive acute inflammatory response in the lung parenchyma, leading to alveolar oedema, decreased lung compliance and, ultimately, hypoxaemia. **Some population, in healthy condition, for instance Tibetan, live in hypoxic hypobaric conditions without any complication in their respiratory and cardiocirculatory functions. This is possible thanks to their antioxidant defences able to fight the high level of free radicals oxygen produced by low oxygen pressure**. This ability is attributed to the high use of polyphenols in the diet (Owen, 2006). Some severe human pathologies arising during infection can be attributed to oxidative stress, and

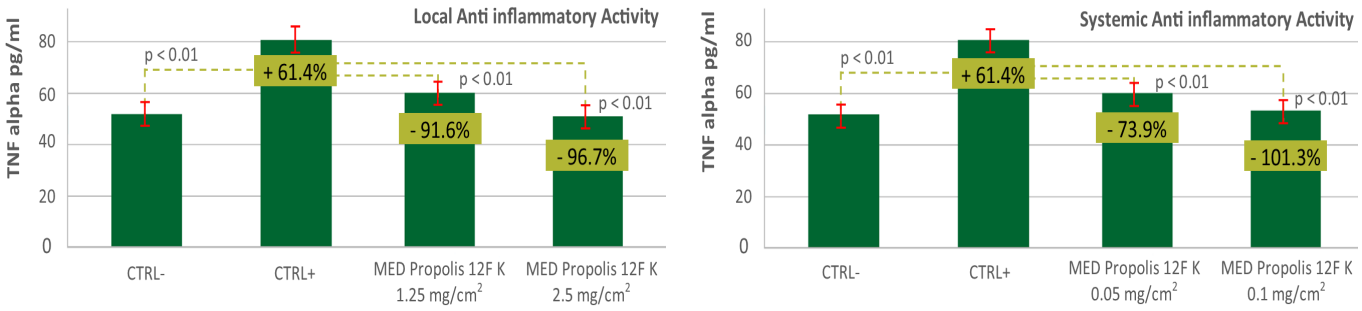
generation of reactive species or uncontrolled inflammation during infection can even have fatal consequences. Hence, there is a need for nutritional interventions to limit or control both oxidative stress and inflammatory reactions, and in turn, the role of dietary fatty acids and antioxidants is described in accordance with the effect on immunity. **During an infectious disease, or oxidative stress, injury, or presence of toxins, it is crucial that the developed free radicals are scavenged and detoxified into harmless products**.

The initial levels of defence are the watersoluble antioxidant enzymes (GSH-PX, superoxide dismutase (SOD), and catalase (CAT) and metal-binding proteins). Curti et al. (2019) demonstrated that M.E.D. Propolis can improve the endogenous antioxidant defence in vivo enhancing the expression level of SOD and CAT as reported in figures.

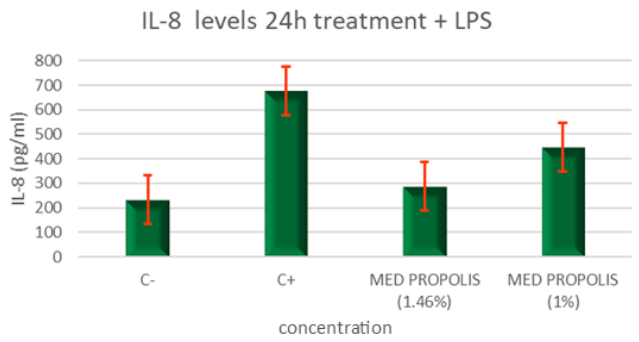


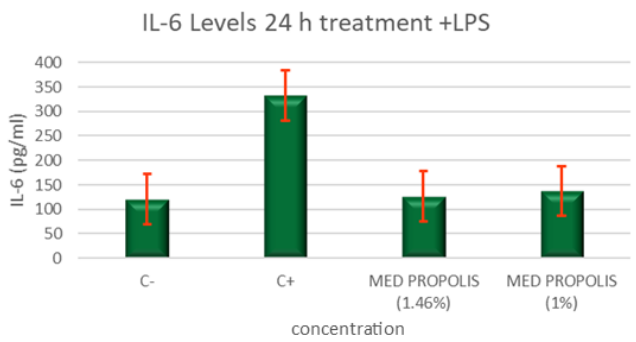
The average CAT and SOD-1 concentration in the control group and in mice treated with different dosages of propolis expressed in pg/mg of soluble liver protein. A significant difference could be detected after the prolonged treatment, with 250 mg/kg of propolis extract compared to the control (means a p = 0.0106)*

M.E.D. Propolis show a good ability to reduce the proinflammatory cytokines level through an epigenetic mechanism of action *in vitro* and, thanks to its good bioavailability, to enhance the endogenous antioxidant defence *in vivo*. Moreover, in human, M.E.D. Propolis resolved topic inflammatory diseases promoting the restore of the symptoms related to URTIs also in non bacterial infections. This suggest that M.E.D. Propolis works on virus and inflammation (Esposito et al., 2020). In other *in vitro* studied, M.E.D. Propolis showed its local and systemic anti inflammatory activity acting on TNF-α, IL-6, IL-8 expression level as shortly shown in figures below.



Dosage on TNF-α in cell culture CTR-, CTR+ and treated with tested product. The results are expressed as mean value ± s.e. (expressed in pg/ml) and as % variation (mean value ± s.e.) compared to CTR- ; anti-inflammatory activity is expressed as reduction od cytokine compared to CTR+ .





*Effect on the production of IL-8 and IL-6 induced by the treatment (24 h) on HaCat cells with two different concentrations of M.E.D. PROPOLIS in the presence of LPS. C-: negative control (untreated cells) (n=1; replicates=2, plate analysed three times). * $p \leq 0.05$ and ** $p \leq 0.01$ were statistically significant compared to cells treated with LPS (C+).*

Thanks to these scientific evidences, M.E.D. Propolis confirms the wide literature data on anti inflammatory and antioxidant activity of polyphenols. Moreover, M.E.D. Propolis can help the body against the pathogens and opportunistic bacterial infections. The main difference between M.E.D. Propolis and other sources of polyphenols or other propolis extract is the standardization of M.E.D. Propolis, the integrity of polyphenol complex from propolis, the richness in active compounds that make it an unique product (Zaccaria et al., 2019).

Conclusions

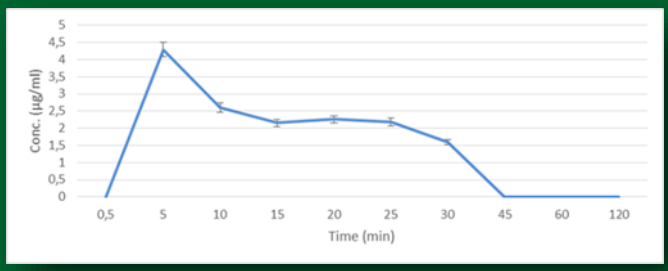
The local and systemic use of a rich source of polyphenols such as M.E.D. Propolis could help the body to reinforce the immune system, modulate the endogenous antioxidant and anti inflammatory system and regulate the anti inflammatory response after viral or bacterial infections.

M.E.D. Propolis, thanks to its standardization, differentiation in pharmaceutical forms and scientifically proved activity, could support the total protection of the body.

How B Natural helps you

To offer a unique range of products with several demonstrated activities in enhancing natural immune response. Thanks to different forms available, from water dispersible powder to alcoholic and oily liquids, is possible to formulate oral sprays, suspensions, softgels, oral dispersible tablets, oral dispersible sachets, lozenges, hard gelatin capsules .

To modulate the immune system and the anti inflammatory response the best products are the ESIT extracts to produce capsules and soft gels. This product is easy to manage during the production and has a good bioavailability as demonstrated by Curti et al. (2019) and increase the antioxidant defence (SOD, CAT) in *in vivo* test.



Galangine–glucuronide concentration in plasma samples collected at different times is shown: after 5 min this metabolite reaches its highest concentration in plasma; then, the concentration maintains a plateau; finally, after 45 min from the treatment, it is no longer detectable. Asterisk indicates significantly different from the other time points ($p < 0.05$).

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