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Research Article

Effects of hydroxymethylfurfural from chemical-protein interaction networks in Apis mellifera, Bos taurus and Homo sapiens species

Efeitos do hidroximetilfurfural a partir de redes de interação químico-proteínas nas espécies Apis mellifera, Bos taurus e Homo sapiens

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ABSTRACT

Hydroxymethylfurfural (HMF) is a compound used as an indicator of food and feed quality. Its concentration can vary according to storage and processing conditions, being influenced by factors such as temperature, pH, and storage time. HMF has antioxidant, anti-inflammatory, and anti-hypoxic properties, and can protect cells against oxidative damage. However, at high concentrations, HMF can be cytotoxic, mutagenic and carcinogenic, which denotes the need to understand its mechanisms of action in different organisms. In this study, chemical-protein interaction networks were constructed, within the scope of bioinformatics, to analyze the effects of HMF on Apis mellifera, Bos taurus and Homo sapiens. In bees, HMF interacts with proteins such as GB17880-PA and LOC551167 that are associated with multi-drug resistance and molecule transport, suggesting a role in defending against oxidative stress. In cattle, HMF interacts with proteins such as CYGB and SDHA, involved in respiratory functions and energy production, also indicating potential protective effects against oxidative damage. In humans, HMF acts on proteins such as HBB and SULT1A2, related to hormone metabolism and immunity, with effects that vary according to the dosage and metabolic pathway activated. According to the results found, it is observed that HMF can modulate important biological processes, such as oxidative phosphorylation, purine metabolism and cell signaling. However, in vitro and in vivo functional studies are necessary to confirm these interactions and elucidate the molecular mechanisms involved.

KEYWORDS: Bioinformatics analysis. Leading molecules. KEGG pathways. Molecular mechanism. STITCH.. Lead molecules. KEGG pathways. Molecular mechanism. STITCH.

RESUMO

O hidroximetilfurfural (HMF) é um composto utilizado como indicador de qualidade em alimentos para humanos e animais. Sua concentração pode variar de acordo com as condições de armazenamento e processamento, sendo influenciada por fatores como temperatura, pH e tempo de armazenamento. O HMF apresenta propriedades antioxidantes, anti-inflamatórias e anti-hipóxicas, podendo proteger células contra danos oxidativos. Contudo, em altas concentrações, o HMF pode ser citotóxico, mutagênico e carcinogênico, o que denota a necessidade de compreender seus mecanismos de ação em diferentes

organismos. Neste estudo, redes de interação químico-proteína foram construídas, no âmbito da bioinformática, para analisar os efeitos do HMF em *Apis mellifera*, *Bos taurus* e *Homo sapiens*. Em abelhas, o HMF interage com proteínas como a GB17880-PA e a LOC551167 que estão associadas à resistência a múltiplas drogas e ao transporte de moléculas, sugerindo um papel na defesa contra estresse oxidativo. Em bovinos, o HMF interage com proteínas como a CYGB e a SDHA, envolvidas em funções respiratórias e produção de energia, também indicando possíveis efeitos protetores contra danos oxidativos. Já em humanos, o HMF atua sobre proteínas como a HBB e a SULT1A2, relacionadas ao metabolismo de hormônios e à imunidade, com efeitos que variam conforme a dosagem e a via metabólica ativada. De acordo com os resultados encontrados, observa-se que o HMF pode modular processos biológicos importantes, como a fosforilação oxidativa, o metabolismo de purinas e a sinalização celular. No entanto, são necessários estudos funcionais *in vitro* e *in vivo* para confirmar essas interações e elucidar os mecanismos moleculares envolvidos.
PALAVRAS-CHAVE: Análise bioinformática. Moléculas líderes. Vias KEGG. Mecanismo molecular. STITCH.

INTRODUCTION

Hydroxymethylfurfural (HMF) content is used as a parameter in quality control of different food items, such as honey, milk, and animal feed (OBA et al. 2022, SHAPLA et al. 2018, FALLICO et al. 2004). When stored in suitable conditions inside or outside the hive, honey has very low concentrations of HMF (KRAINER et al. 2016). However, inadequate heating or storage can lead to considerably high levels of HMF (TOSI et al. 2001, KARABOURNIOTI & ZERVALAKI 2001). Studies also show a trend toward increased HMF levels in products subjected to long storage periods, especially at high temperatures (SHAPLA et al. 2018, KAMBOJ et al. 2019). Other factors, such as acidity, moisture, sugar content, and honey origin, can also favor the increase in HMF levels (KAMBOJ et al. 2019).

In milk, heating during processing or improper storage can stimulate the production of HMF by the Maillard reaction due to the presence of reducing sugars and lysine-rich proteins (ALBALÁ-HURTADO et al. 1997). For this reason, HMF is often used as an indicator of uncontrolled long-term warming of dairy products (XING et al. 2020, XING et al. 2021).

In the context of animal husbandry, thermal feed processing, used to improve safety, shelf life, nutritional properties, feed texture and nutrient digestibility (KAUSHIK 2015, DHAKAL & ALDRICH 2022), can, under specific conditions, favor the formation of HMF (CAPUANO & FOGLIANO 2011).

Due to the presence of HMF in food for human and animal nutrition, it is necessary to understand the effects of this substance in different species, as the literature is controversial regarding the presence of this compound in food (GLATT et al. 2005, MONIEN et al. 2012, ZHAO et al. 2013, YAMADA et al. 2011, KITTS et al. 2012, LI et al. 2011, LIN et al. 2012). In this context, interaction networks, in the field of bioinformatics, are important tools to predict interactions between chemical compounds and their targets elucidating molecular mechanisms involved in physiological and/or pathological conditions (AHMAD et al. 2024).

Therefore, this study focused on investigating molecular mechanisms involved in the acting of HMF in Apis mellifera, Bos taurus and Homo sapiens organisms, through the construction of chemical-protein interaction networks.

MATERIAL AND METHODS

The chemical-protein interaction networks were obtained from the STITCH platform, version 5.0 available at http://stitch.embl.de/. To initiate the construction of networks, HMF was used as an input descriptor, selecting the species Apis mellifera, Bos taurus and Homo sapiens, in the organism field. The configuration was the same for all networks, following the parameters shown in Figure 1.

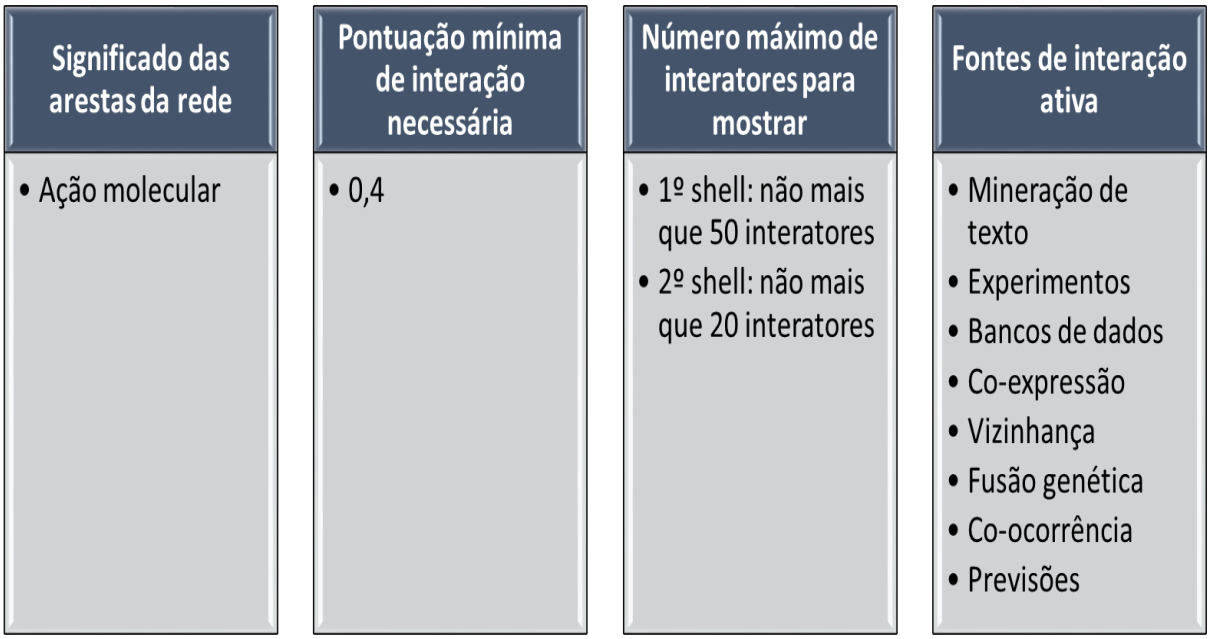

Figure 1. Parameters for configuration of networks constituted from the HMF molecule in the organisms Apis mellifera, Bos taurus and Homo Sapiens.

The molecules with the highest number of interactions in the networks were characterized as leaders. The leading molecules were defined by the sum of the combined score of each molecule in nodes 1 and 2 (molecules with the highest score at the end of the sum were determined as leaders). The data obtained in the chemical-protein interaction networks were compared and discussed based on reports in scientific literature.

The literature review used the following dynamics for searching information: i) general performance of HMF on the different species. ii) function of molecules that appeared bound to HMF in the interaction network. iii) action of molecules in the respective species. iv) relationship of molecules with HMF. v) description of the pathway involved. vi) description of pathways in the respective species. vii) relationship between pathways and HMF. The discussion of the results obtained in the in-silico analyses was based on this literature review.

RESULTS AND DISCUSSION

In the chemical-protein interaction networks, elaborated in the different organisms, the interaction of HMF with different proteins can be perceived. To this interaction, was given confidence scores ranging from medium to high (Figure 2).

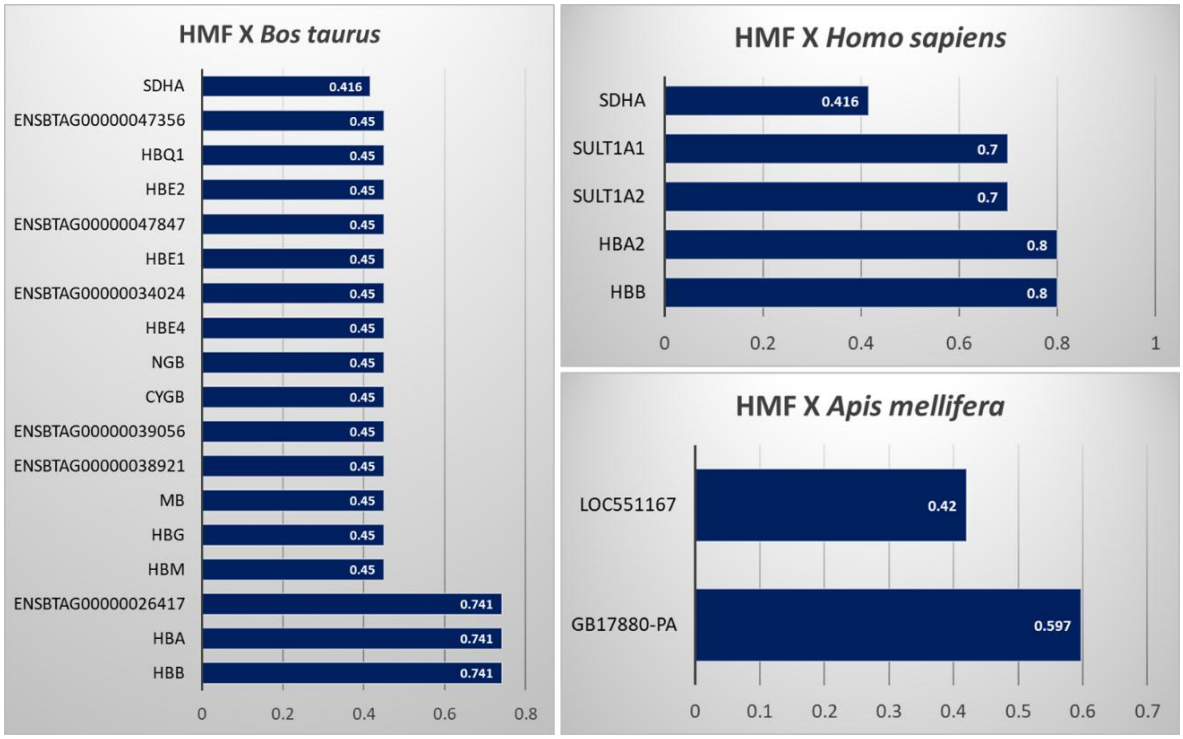

Figure 2. Representation of protein binding score to HMF in chemical-protein interaction networks in Bos taurus, Homo sapiens and Apis mellifera. Medium score = 0.4. High score = 0.7. Very high score = 0.9.

In Figure 3 it is possible to see that, in Apis mellifera species, HMF can interact directly with GB17880-PA (uncharacterized protein) and LOC551167 (GB13224-PA) proteins (homologous of 49-like multiple resistance protein).

GB17880-PA is an uncharacterized protein (i.e., part of genomic and proteomic data, however, it has no known function and is not experimentally characterized). It is important to understand that the characterization of proteins with unknown functions is relevant for the elucidation of the molecular mechanism involved in the action of HMF in Apis mellifera species (KOONIN & GALPERIN 2002). Therefore, the role of HMF through GB17880-PA can be positive or negative depending on the characterization of the function of this macromolecule. In principle, the interaction confidence score of 0.597 denotes a connecting function with HMF (medium confidence score).

The LOC551167 protein, in turn, is known as the 49-like homologous multidrug resistance protein. It was found in literature that this protein is involved with the KEGG pathway "ABC Transporter". This transporter translates membrane-bound proteins. It also plays a role in translation, ribosome assembly, and cell signaling (STURM et al. 2009).

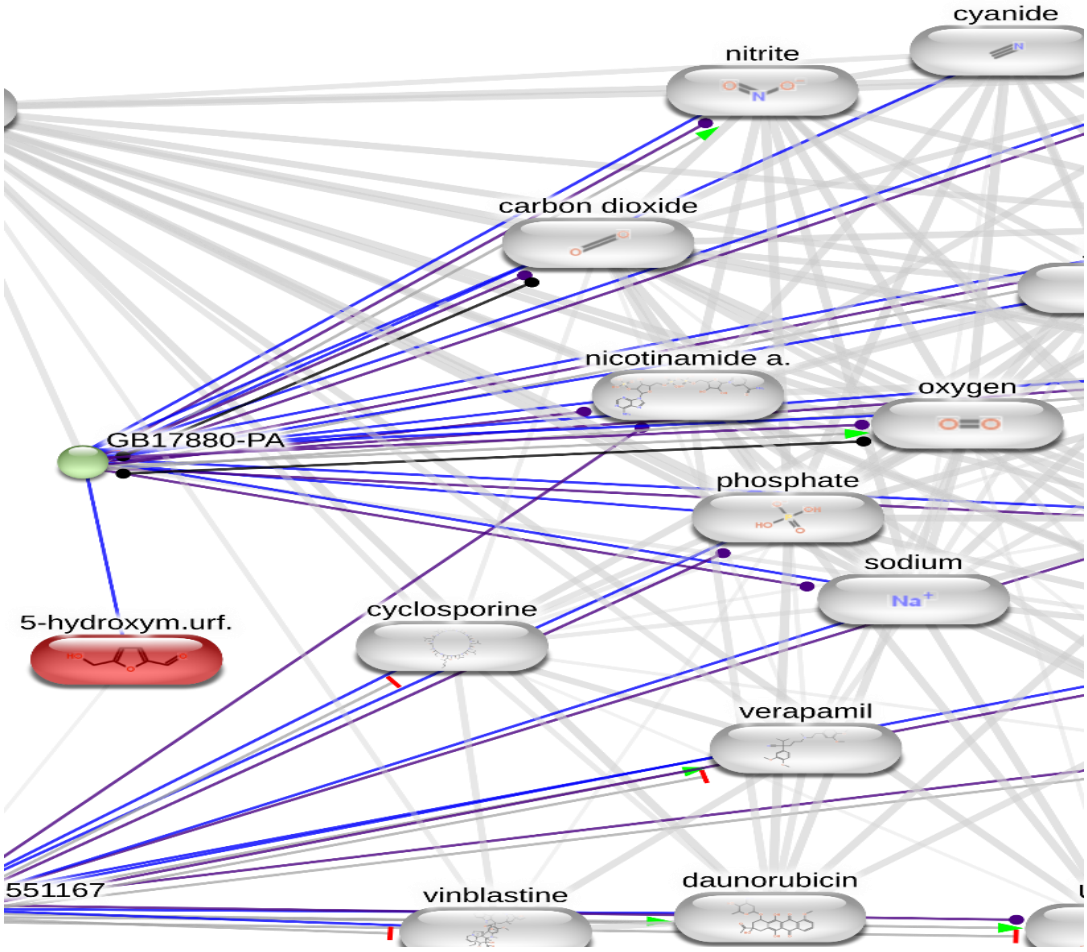

Figure 3. Hydroxymethylfurfural interaction network in Apis mellifera species. Lines and, for the directed edges, arrows of different colors, represent different types of edges in the action outlook: binding (blue), activation (green), inhibition (red), catalysis (magenta), same activity (cyan), and reaction (black).

The interaction between HMF and LOC551167 protein suggests that bees have defense mechanisms against the effects of HMF, since this protein confers resistance to multiple chemical compounds in the body. In this context, ATP-binding cassette transporters (ABCs) classified from ABCA to ABCH, in which the protein LOC551167 acts, are important in insect detoxification (DERMAUW & VAN LEEUWEN 2014).

ABC transporters have been studied extensively in the context of multidrug-resistant human pathogens (GOTTESMAN et al. 2002). However, research on bees is scarce. One study showed evidence of the importance of multidrug-resistant transporters in the detoxification of acaricides and neonicotinoids (HAWTHORNE & DIVELY 2011). In addition, it was reported that two genes associated with multidrug resistance were upregulated in bees fed with p-coumaric acid (MAO et al. 2013). Another important point to be observed in this aspect is that, since HMF is associated with proteins involved in multidrug resistance, it is possible that HMF activates the system, enhancing the resistance of bees to insecticides.

Still in the built interaction network (Figure 3), it was found that the lead molecule was MgATP (Adenosine Triphosphate). GB17880-PA and LOC551167 proteins interact with the lead molecule by bridging the gap between HMF and MgATP. This interaction

indicates that these proteins play a mediating role in the effects of HMF by connecting it to MgATP-dependent biochemical processes, which may signal its participation in defense or detoxification mechanisms in bees.

Cellular and extracellular adenosine 5'-triphosphate (ATP) act as energy transporter in different cellular functions and activating nucleotide receptors, respectively (JUNGER 2011, IDZKO et al. 2014). Adenosine, in turn, is a regulatory metabolite, produced in response to pathophysiological processes, and triggers several signaling events (JOHNSTON-COX et al. 2010).

Therefore, it is noticeable that HMF can trigger a cascade of effects on bees through the modulation of the MgATP molecule, as proposed in Figure 4. In the interaction network for the Apis mellifera species, MgATP, in addition to having significant roles in metabolism, is a neurotransmitter (STITCH 2024).

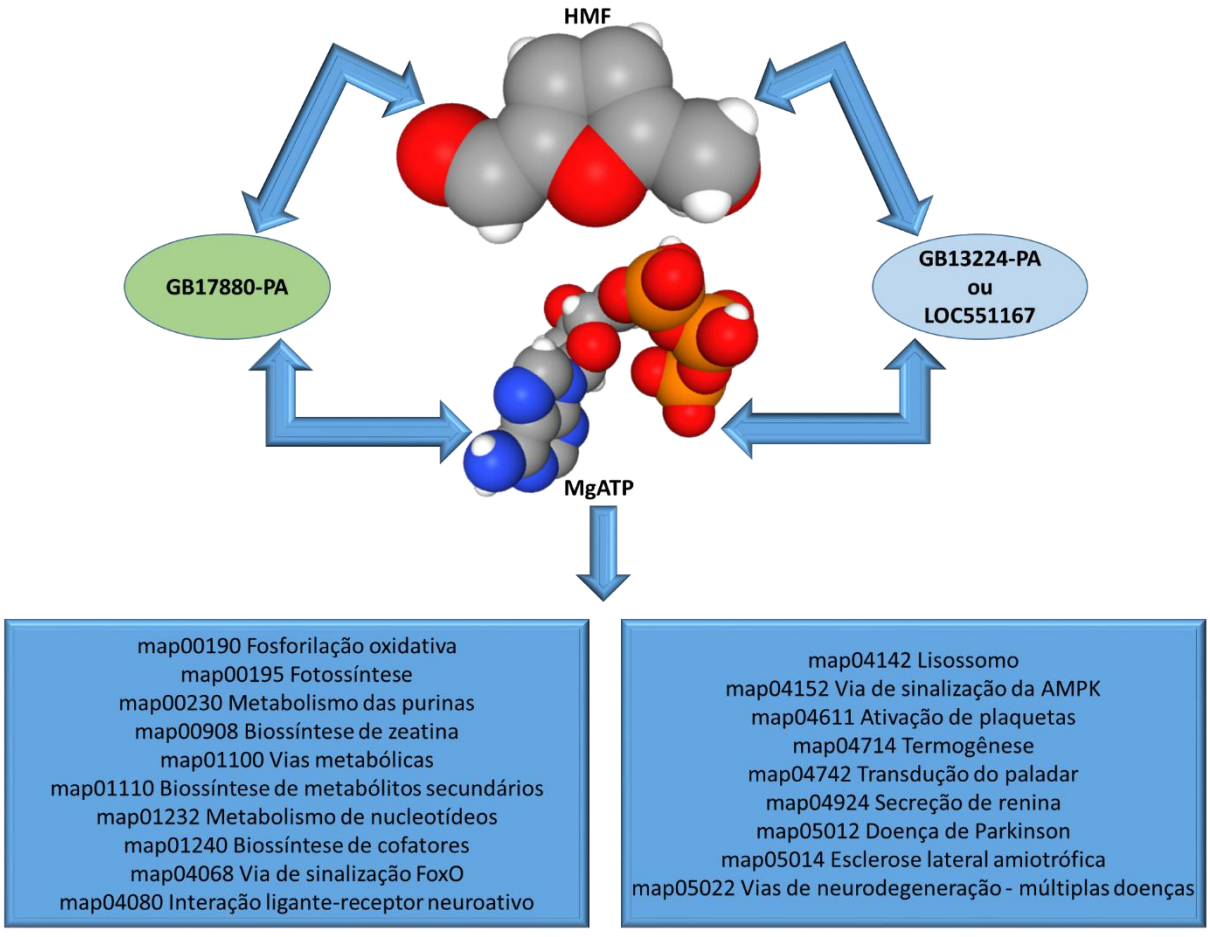

Figure 4. Proposal for HMF mechanism action in Apis mellifera species.

The action of HMF on the species Apis mellifera by means of the leader molecule MgATP can trigger different pathways, as shown in Table 1. These pathways may be responsible for the positive or negative effects of HMF on bees. In the literature review done by SHAPLA et al. (2018), it was pointed out that HMF, as a constituent of processed foods, provides adverse and beneficial effects on human and bee health.

Table 1. Pathways of HMF on Apis mellifera bees, evidencing the positive and negative effects on this species.

Pathway	Effect	Pathway	Effect
map00190 Oxidative phosphorylation	Positive	map04142 Lysosome	Indeterminate
map00195 Photosynthesis	Not applied	map04152 AMPK signaling pathway	Indeterminate
map00230 Purine metabolism	Positive	map04611 Platelet activation	Not applied
map00908 Zeatin biosynthesis	Not Applied	map04714 Thermogenesis	Not applied
map01100 Metabolic pathways	Positive or negative	map04742 Palate transduction	Indifferent
map01110 Biosynthesis of secondary metabolites	Not Applied	map04924 Renin secretion	Not applied
map01232 Nucleotide metabolism	Positive or negative	map05012 Parkinson's disease	Not applied
map01240 Cofactor biosynthesis	Indeterminate	map05014 Amyotrophic lateral sclerosis	Not applied
map04068 FoxO signaling pathway	Indifferent or negative	map05022 Neurodegeneration pathways – multiple diseases	Positive
map04080 Neuroactive ligand-receptor interaction	Positive	-	-

The oxidative phosphorylation pathway (map00190) is the stage of cellular respiration with the highest energy gain for the cell, in which NADH and FADH2 can be oxidized in the protein complexes of the mitochondrial crests. (TERUYO et al. 1996). Increased oxidant production can negatively interfere with this pathway (MAGALHÃES et al. 2005, ZOU et al. 2014, ZOU et al. 2015). In this context, HMF can act as an antioxidant, since reactive groups within the furan ring attract electrons (LI et al. 2011a, SHAPLA et al. 2018). Corroborating these studies, CIARLONE et al. (2023) observed that mitochondrial membrane depolarization, controlled superoxide production in animals treated with HMF.

The increase in production of oxidizing molecules is among the causes of the aging process that affect bees and other animals (HARMAND 1956, CROSS et al. 1987). CERVONI et al. (2017) showed that oxidative parameters and differential expression of genes related to these processes are distinct between nursing and forage worker bees, and also in relation to the body compartment. Therefore, HMF can play an important role in the different stages of bees' lives, favoring their strength and aptitude to perform different activities.

The purinergic system (map00230) performs biosignaling between cells, acting in the functioning of the whole organism (CARDOSO et al. 2021). This biosignaling pathway regulates the immune response, inflammatory processes, platelet aggregation, cell proliferation and death (JOHNSTON-COX et al. 2010). Some studies have shown the enrichment of purine metabolism pathway in bees (ZHANG et al. 2022, XU et al. 2024).

HMF is known to exert an anti-inflammatory effect by inhibiting the activity of xanthine oxidase (LIN et al. 2012), a critical enzyme that catalyzes the purine catabolic pathway. This corroborates the indication of the antioxidant effect of HMF, since the enzyme xanthine oxidase is an endogenous producer of superoxide (LORNE et al. 2008). Thus, in the context of contamination of a hive by pesticide, which causes oxidative stress, HMF can be an important defense, since the responding genes and metabolites perform functions related to purine and pyrimidine metabolism (GAO et al. 2022).

It is important to understand that a metabolic pathway consists of a series of connected chemical reactions that feed into others. The global metabolic pathway map (map01100), the largest KEGG pathway map, features 370 modules with specific metabolic functions (KANEHISA et al. 2021). Therefore, studies that analyze the relationships between HMF and metabolic pathways can identify positive or negative effects on bees depending on the acting paths.

The nucleotide metabolism pathway (map01232) is related to the growth of parasympathetic neurons (NANGLE & KEAST 2011) and DNA damage in the liver (LI et al. 2019). Although no studies were found reporting the action of HMF in this pathway for the Apis mellifera species, in yeasts it was demonstrated that HMF reduces the specific growth rate (ASK et al. 2013), modulating genes involved in the nucleotide metabolism pathway and others (REGENBERG et al. 2006). On the other hand, genes involved in environmental stress response were upregulated by HMF (ASK et al. 2013). These results denote that HMF can influence different phenotypes (growth activation or inhibition, for example).

In the metabolic process, cofactors play an important role in enzymatic activities. It can be divided into metal ions and organic molecules called coenzymes (KIRSCHNING 2022). The understanding of cofactor chemistry (map01240) is directly related to the production of vitamins by fermentation and the exploration of biosynthetic enzymes of cofactors as antibiotic targets (BEGLEY et al. 2008). Thus, to determine whether HMF exerts a positive or negative effect on bees using the cofactor biosynthesis pathway, it is necessary to specify a pathway, given the diversity of chemical reactions involving the cofactors. For example, bees are known to have enzymes, such as P450 (composed of an apoenzyme and a non-protein cofactor), which plays a role in detoxifying chemical compounds, such as HMF, in bees (JOHNSON et al. 2013).

The FoxO signaling pathway (map04068), which includes the forkhead box (Fox) gene family, participates in the control of gluconeogenesis and glycogenolysis (TEANEY & CYR 2023, NIE et al. 2018). According to KIYA et al. (2008), a Fox gene was identified in the brain of Apis mellifera, and its expression in the brains of worker bees was increased after hatching, suggesting a role for the gene in the development and maturation of worker brains. From this perspective, activation of the Fox signaling pathway reinforces the role of insulin signaling pathways in mediating neuronal function and behavior in insects (WU & BROWN 2005, RITTSCHOF et al. 2015).

Although no studies have been verified on the action of HMF in this pathway in bee species, in mice with diabetes and liver injury, HMF did not interfere with blood glucose and lipid levels, but positively modulated liver function (LU et al. 2021). While in Drosophila melanogaster, HMF caused oxidative stress, disrupted glucose and lipid metabolism, and induced intestinal damage by damaging related signaling pathways, affecting the development of this insect (LU et al. 2021).

Regarding the neuroactive ligand-receptor interaction pathway (map04080), literature emphasizes that this pathway involves a set of receptors located in the plasmatic membrane, playing a role in the regulation of neuronal plasticity, as well as

in the learning and memory processes, as highlighted by SU et al. (2009). HUANG et al. (2023) showed the importance of this pathway in olfactory learning and memory in bees.

Supporting these reports, it was observed that pre-exposure of Kunming mice to HMF (100 µg/ml, 1 h) attenuates damage to the blood-brain barrier and hippocampal neurons under hypobaric hypoxia conditions (LI et al. 2011a). Under these conditions, HMF increased survival capacity by acting as a therapeutic against neuronal disorders (LI et al. 2011b). Therefore, under specific conditions, it is suggestive that HMF acts positively on the nervous system of bees through the neuroactive ligand-receptor interaction pathway.

Lysosomes (map04142) are membrane-bounded organelles in animal cells that serve as the cell's primary digestive compartment, to which all types of macromolecules are delivered for degradation (KEGG PATHWAY 2025a). In the literature consulted, no information was found on the degradation or accumulation of HMF in the bees' bodies. However, a study by GREGORC et al. (2019) pointed out that the cytotoxic effect of HMF depends on the dosage of digestion by bees.

These findings demonstrate that HMF escapes the action of the lysosomal system of bees. In humans, in turn, HMF is completely eliminated via urine after 48 hours of its oral administration (HARDT-STREMAYR et al. 2013, PRIOR et al. 2006). Therefore, the metabolism, biotransformation and excretion of HMF, and thus the rate of clearance from the body, depends on an individual's organic function (ULBRICHT et al. 1984).

The AMPK signaling pathway (map04152), in turn, acts on eukaryotic cells under low energy conditions, being activated when high and low levels of adenosine triphosphate (ATP) and adenosine monophosphate (AMP) occur, respectively (HARDIE et al. 2003). Studies that show any type of action by HMF on this route are scarce in the literature.

The Palate transduction pathway (map04742) plays a fundamental role in the recognition and selection of beneficial and harmful foods by animals (FABER et al. 2006). The basic flavors, bitter, sweet, sour, and salty, are recognized by humans and most other animals (KEGG PATHWAY 2025b). Studies show the importance of metabolic pathways involved in smell and taste functions for the adaptation of insects to different environments (SU et al. 2023, YANG et al. 2022). Taste is essential for bees to choose suitable food sources, resins, water sources, and recognition of nestmates. Interestingly, when bees are free to express aversion behaviors, they reject highly concentrated bitter and saline solutions (SANCHEZ 2011). Therefore, it is possible to suspect that bees reject high concentrations of HMF, due to the possibility of having an unusual taste.

Neurodegeneration pathways (map05022) are generally defined as progressive and irreversible loss of neurons, which can affect the peripheral or central nervous system (ERKKINEN et al. 2018, MOT et al. 2018, KEGG PATHWAY 2025c). Although studies on human neuropathologies have advanced in recent years, the same has not

happened for bees. MORFIN et al. (2021) report that bee neuropathologies are associated with reduced grooming behavior due to sublethal exposure to specific chemical compounds. As previously explained, HMF seems to have a protective effect on the nervous system of bees by reducing oxidative stress and free radical formation, among other mechanisms (LI et al. 2011, SHAPLA et al. 2018, CIARLONE et al. 2023).

In the species Bos taurus, HMF shows interaction with different proteins such as CYGB (Cytoglobin), NGB (Neuroglobin), MB (Myoglobin), SDHA (Succinate dehydrogenase A), the ones from the ENSBTAG group (most of them non-characterized proteins) and HB (Hemoglobin) (Figure 5).

Coordinated hexaglobins such as CYGB and NGB have been structurally and functionally characterized (CORTI et al. 2016, DE SANCTIS et al. 2004, DEWILDE et al. 2001, SAWAI et al. 2003). Proposed functions for hexaglobins coordinates include redox regulation, O2 sensor function, and enzymatic functions (BLANK et al. 2011b, BURMESTER & HANKELN 2009, KAKAR et al. 2010). Penta-coordinated globins such as HB and MB play respiratory roles in the transport and storage of O2 (BLANK et al. 2011a, LÜDEMANN et al. 2019, MAIRBÄURL & WEBER 2012, WEBER & FAGO 2004). SDHA (succinate dehydrogenase) acts in the transfer of electrons, generating a proton gradient used for the synthesis of ATP, providing energy to the cells (RUTTER et al. 2010). Therefore, depending on the functions of each of the proteins that interact with HMF, it is possible to predict that this molecule modulates important functions in the species Bos taurus.

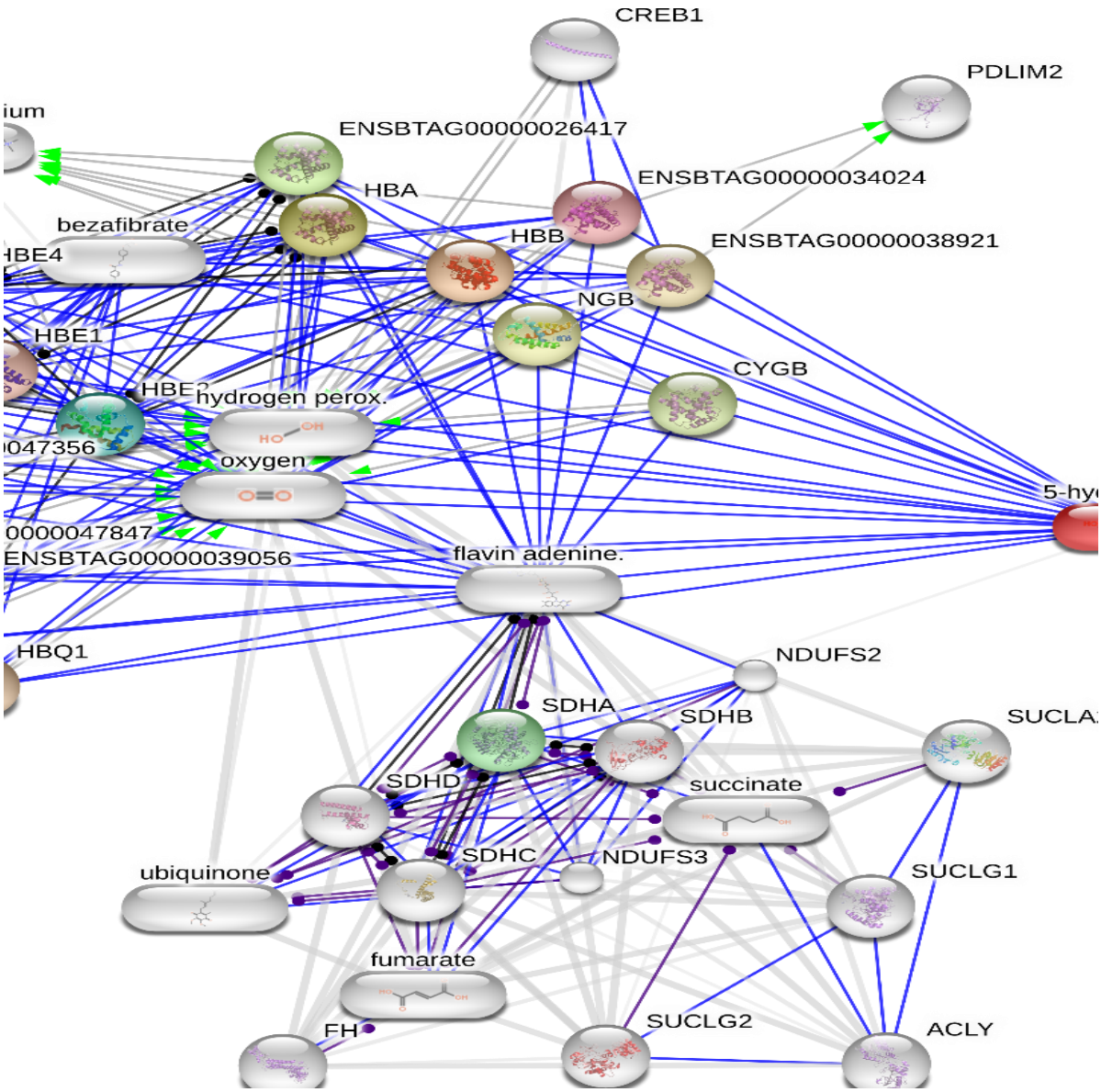

Figure 5. Hydroxymethylfurfural interaction network in the Bos taurus species. Lines and, for the directed edges, arrows of different colors, represent different types of edges in the action outlook: binding (blue), activation (green), inhibition (red), catalysis (magenta), same activity (cyan), and reaction (black).

The molecule that presented a greater number of interactions in the species Bos taurus was adenine flavin, defined as the leading molecule in this network. Among the proteins that interact with adenine flavin are those targeted by HMF. Therefore, one possibility of HMF acting on the species Bos taurus is through Adenine flavin, as shown in Figure 6.

Adenine flavin dinucleotide is a condensation product of riboflavin and adenosine diphosphate (STITCH 2024). It is a cofactor for cytochrome-b5 reductase, the enzyme that keeps hemoglobin in its reduced functional state, and for glutathione reductase, an enzyme that also protects erythrocytes from oxidative damage (BOES & DURHAM 2017). In synergism with adenine flavin, HMF, which covalently binds to hemoglobin, provides high permeability of the red blood cell membrane, where it increases the affinity of hemoglobin for O2 (ABDULMALIK et al. 2005). Another study

established that HMF produces modification of the oxygen affinity of hemoglobin with promising therapeutic potential to increase O2 delivery during hypoxia (LUCAS et al. 2019).

Figure 6 shows a possible action of HMF in the Bos taurus species through KEGG pathways, in which Adenine flavin is involved.

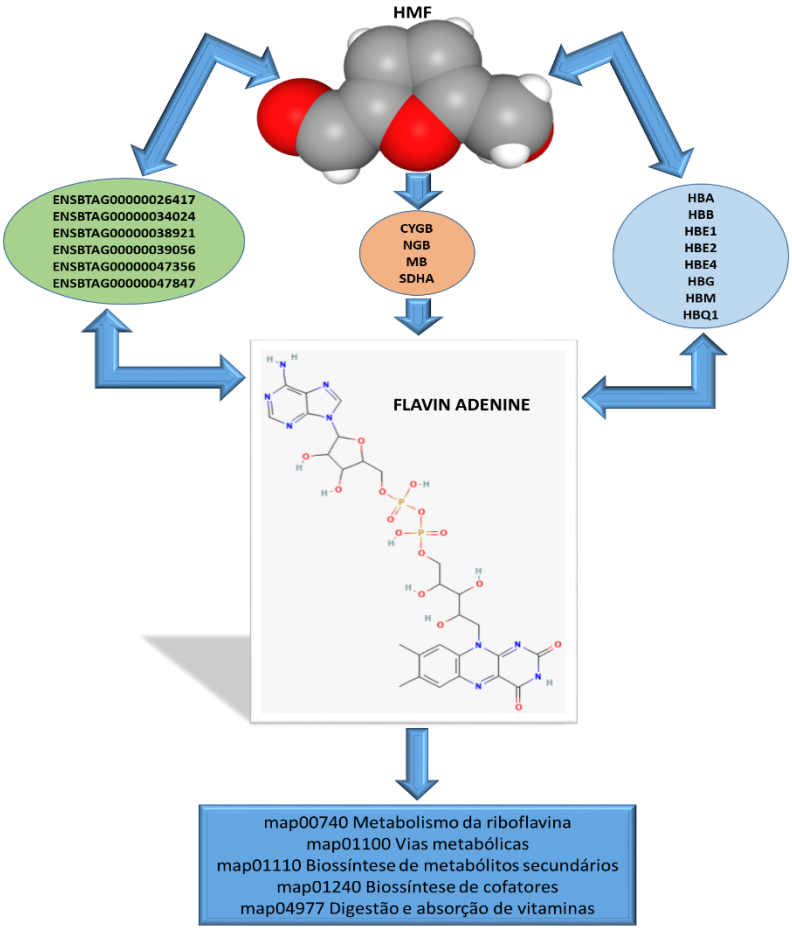

Figure 6. Proposal for HMF action in the Bos taurus species.

In this sense, HMF can exert positive and negative effects, as shown in Table 2.

Table 2. Pathways of HMF on Bos taurus species, evidencing the positive and negative effects of this species.

Pathways	Effect	Pathway	Effect
map00740 Riboflavin metabolism	Positive	map01240 Cofactor biosynthesis	Indeterminate
map01100 Metabolic pathways	Positive or negative	map04977 Digestion and absorption of vitamins	Indeterminate
map01110 Secondary metabolites biosynthesis	Not applied	-	-

In addition, it is hypothesized that HMF can act on mammalian species, such as Bos taurus, via riboflavin metabolism (map00740). Riboflavin is a precursor to important coenzymes such as FAD and FMN, which participate in the electron transport chain (POWERS 2003, EDWARDS et al. 1999, MERRILL et al. 1981).

Interestingly, riboflavin can act by activating or inhibiting oxidative stress, through the production of superoxide and reduction of hydroperoxides, respectively (MASSEY 2000). In addition, riboflavin has been correlated with the signal transduction mechanism of apoptotic cells, as well as in the control of biological rhythms (MASSEY 2000). HMF, in this context, showed antioxidant and anti-ischemic effects (WEN et al. 2010), improved acute liver injury (DING et al. 2008) and inhibited oxidative damage to hepatocytes (WEN et al. 2010). All of this suggests the anti-apoptosis mechanism of HMF.

Studies suggest that HMF may be a useful compound for preventing damage to neurons during oxidative stress. The neuroprotective effects of HMF may be related to resistance to apoptosis and antioxidant effect (GU et al. 2013).

Regarding the digestion and absorption of vitamins (map04977) pathway it was observed that HMF content is associated with the composition of food and other factors such as pH, water activity, temperature, fermentation agent and time (NGUYEN et al. 2016). Therefore, the nutritional content of feed that will be given to cattle should be investigated to verify the possibility of consuming a large amount of HMF. On the other hand, focusing on the nutritional value of milk, it is important to investigate whether cow's milk, especially in semi-arid regions that have long periods of high temperatures, is subject to contain higher amount of HMF due to the ingestion of diets often in conditions of high temperatures.

The interaction network presented in Figure 7 refers to the possibility of HMF acting in the species Homo sapiens. There is a direct interaction of HMF with proteins HBB (Hemoglobin beta), HBA2 (Hemoglobin alpha 2), SULT1A2 (Sulfotransferase 1A2), SULT1A1 (Sulfotransferase 1A1) and SDHA (Succinate dehydrogenase A).

In this network, the lead molecule was also adenine flavin, which interacts with SDHA, HBB, and HBA2 proteins. The beta subunit of hemoglobin (HBB) is an essential component of hemoglobin, playing an important role in innate antiviral immunity (YANG et al. 2019). Hemoglobin A2 (HBA2), representing less than 3% of total hemoglobin in adults, is involved in the diagnosis of beta-thalassemia (STEINBERG & ADAMS 1991, HEAD et al. 2004). Functional studies are necessary to elucidate the modulation capacity of these proteins by the HMF and vice versa.

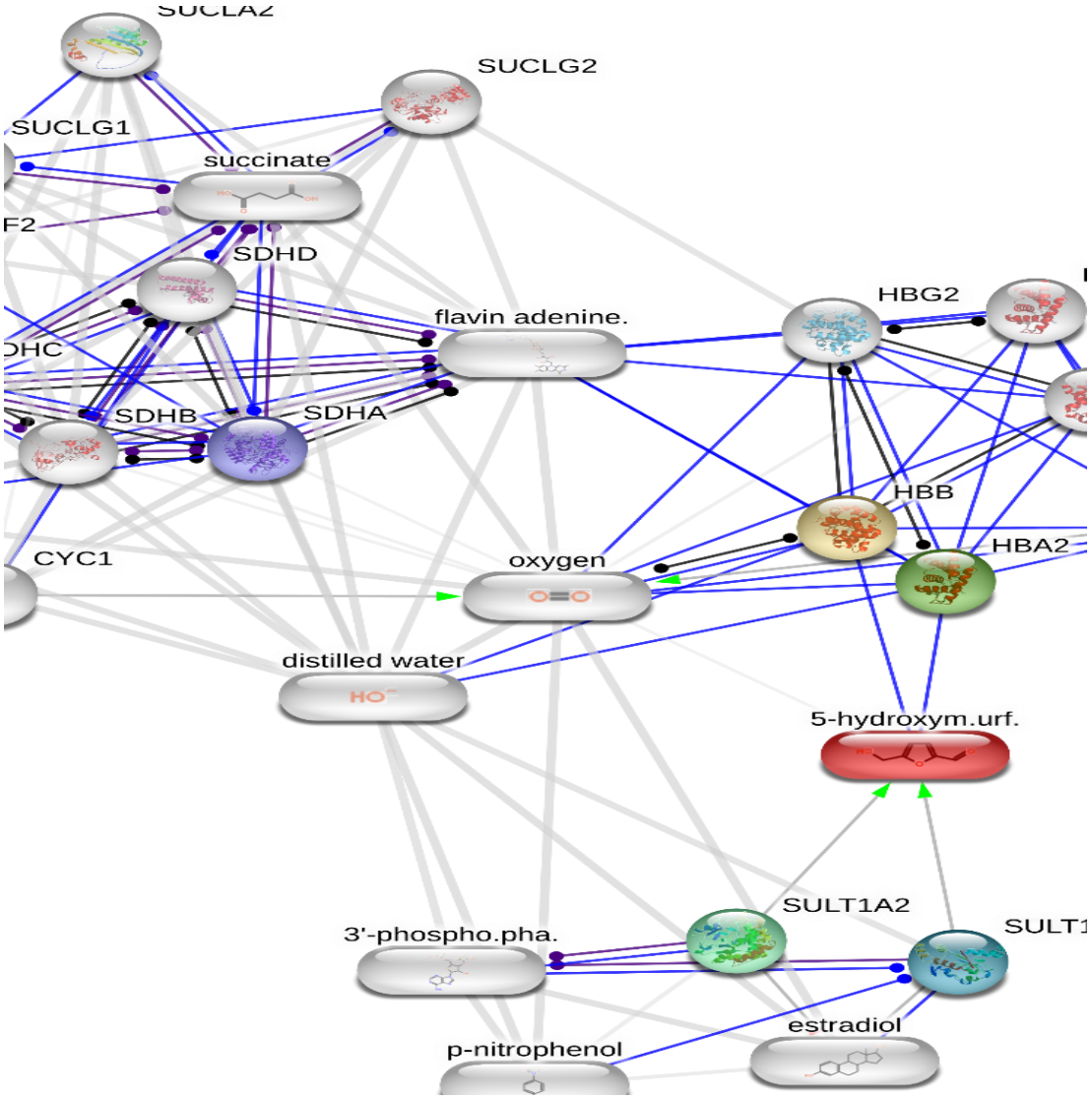

Figure 7. Hydroxymethylfurfural interaction network in the Homo sapiens species Lines and, for the directed edges, arrows of different colors, represent different types of edges in the action outlook: binding (blue), activation (green), inhibition (red), catalysis (magenta), same activity (cyan), and reaction (black).

SULT1A2 encodes a heat-resistant diphenol sulfate-transferase, a key enzyme in sulfuric acid metabolism that catalyzes a variety of hormones (HARRIS et al. 2000, LV et al. 2023). SULT1A1 and SULT1A2 have similar structures and functions and share substrates. Animal studies have shown that dietary fat regulates SULT1A1 gene expression in adipose and liver tissues of obese mice (GUTIERREZ-AGUILAR et al. 2012, LV et al. 2023).

In addition, it has been shown that SULT1A2 gene is highly expressed in healthy liver and may be involved in the pathogenesis of nonalcoholic fatty liver disease (CHATTERJEE et al. 2021, LV et al. 2023). Both enzymes, SULT1A1 and SULT1A2, show high catalytic efficiency using HMF as substrate (GLATT & SOMMER 2006).

However, increased cytotoxic effects have been observed following intraperitoneal administration of Sulfooxymethylfurfural (SMF), which is a metabolite of HMF. Nephrotoxic effects and increased proliferation of hepatocytes were detected

only at high HMF dosage. Thus, the effects of HMF were discrete and not affected by SULT1A1/2 expression (MORANA et al. 2012). Another study hypothesized that the hepatocarcinogenic potential of HMF originates from the formation of mutagenic SMF (MONIEN et al. 2012).

The schematic representation in Figure 8 illustrates the possibilities of action of HMF on the human organism. SULT1A1 and SULT1A2 proteins activate HMF, which in turn interacts with SDHA, HBB and HBA2 proteins, to act on the KEGG pathways of Adenine flavin, in a similar way to what occurs in the Bos taurus species.

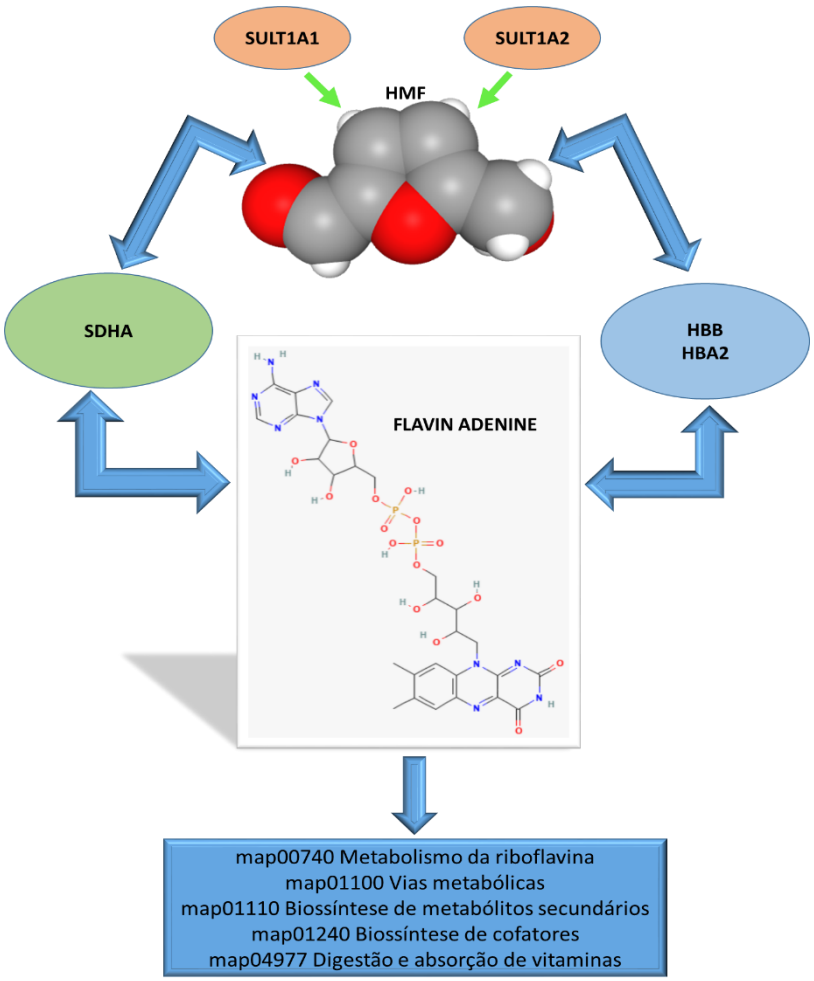

Figure 8. Proposal for HMF action in the Homo sapiens species.

It was notorious that HMF can modulate different molecular pathways in the Apis mellifera, Bos taurus and Homo sapiens species. It is necessary to establish limits and conditions between beneficial and harmful effects, in order to take action to mitigate undesirable effects and efficiently enjoy the benefits of this molecule in different organisms. This study will serve as a basis to guide future research on the molecular mechanisms of HMF in the different species analyzed.

CONCLUSION

Interaction of HMF with proteins in different organisms (Apis mellifera, Bos taurus, and Homo sapiens) demonstrates a network of biological effects that can be positive or negative, depending on the metabolic pathway. In the species Apis mellifera, it is possible to observe that HMF has the potential to modulate defense and detoxification processes, especially through its interaction with proteins such as GB17880-PA and LOC551167, associated with resistance to multiple drugs and transport of molecules. An important hypothesis to be tested in the context of bee resistance to insecticides. In addition, the interaction of HMF with the lead molecule MgATP suggests an important role in the regulation of energy-dependent biochemical processes, such as oxidative phosphorylation and cell signaling, which can positively influence the health of bees under conditions of oxidative stress.

Particularly in the Bos taurus species, HMF interacts mainly with proteins such as CYGB, NGB, MB and SDHA involved in respiratory functions, redox regulation and energy production. The lead molecule Adenine flavin appears to mediate the effects of HMF, suggesting that this compound may act on metabolic pathways related to riboflavin metabolism and cofactor biosynthesis. These interactions may have positive implications in protecting against oxidative damage.

In humans, HMF interacts with proteins such as HBB, HBA2, SULT1A1, and SULT1A2 involved in hormone metabolism and immunity. The activation of HMF by sulfotransferase enzymes can lead to both beneficial effects (protection against oxidative damage) and adverse effects (formation of potentially mutagenic metabolites). Therefore, the effects of HMF on the human body are complex and depend on factors such as dosage, activated metabolic pathway, and physiological state of the individual.

Studies like this are important to understand the molecular mechanisms of HMF in different organisms. However, in silico studies are not conclusive and only raise evidence that needs scientific proof through the conduction of in vitro and in vivo functional studies.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology and formal analysis, Eliane Macedo Sobrinho Santos, Bruna Santos Ribeiro and Anna Christina de Almeida; software and validation, Bruna Santos Ribeiro, Débora Martins Paixão and Hércules Otacílio Santos; investigation, Bruna Santos Ribeiro, Renata Gabriela Chaves Ferreira and Wagner Silva dos Santos; resources and data curation, Janainne Nunes Alves and Sheila Rodrigues Oliveira; writing - preparation of the original draft, Janainne Nunes Alves, Wagner Silva dos Santos and Sheila Rodrigues Oliveira; writing - review and editing, Janainne Nunes Alves, Sheila Rodrigues and Débora Martins Paixão; supervision, Eliane Macedo Sobrinho Santos, Hércules Otacílio Santos and Anna Christina de Almeida; project management, Eliane Macedo Sobrinho Santos and Anna Christina de Almeida;

fundraising, Eliane Macedo Sobrinho Santos and Hércules Otacílio Santos. All authors have read and agreed with the published version of the manuscript.

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STATEMENT OF THE INSTITUTIONAL REVIEW BOARD

Not applicable to studies that do not involve humans or animals.

INFORMED CONSENT STATEMENT

Not applicable as this study did not involve humans.

DATA AVAILABILITY STATEMENT

The data can be made available upon request.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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