

## Review article:

# P-SYNEPHRINE: AN OVERVIEW OF PHYSICOCHEMICAL PROPERTIES, TOXICITY, BIOLOGICAL AND PHARMACOLOGICAL ACTIVITY

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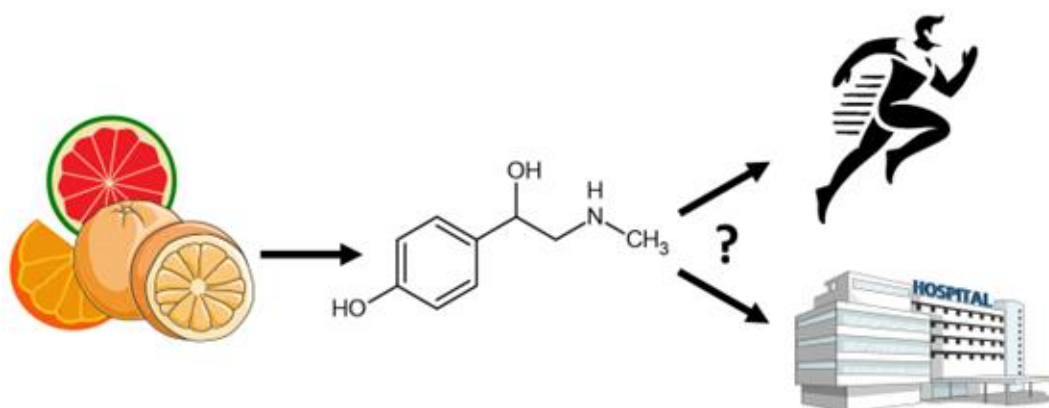


Figure 1: Graphical abstract

## ABSTRACT

p-Synephrine is a popular ingredient in dietary supplements. It is also found in trace amounts in living organisms. It is advertised as a weight loss supplement and it is supposed to improve performance in sports. It is contained in plants of the Citrus family, making it widespread in the human diet. Its pharmacological properties include effects on multiple receptors and signaling pathways. Its effects on the alpha and betanergic systems promote doubts about its safety. There are many studies describing a lack of concern when it comes to the potential harmful effects of this compound. On the other hand, several health incidents associated with p-synephrine use have been reported in the scientific literature, making the toxicity of this compound unclear. This review aims to organize the current knowledge about p-synephrine, including physicochemical characteristics, sources of occurrence, pharmacological effects and possible toxic effects. In addition, the presence of three substitution isomers of the hydroxyl group and one chiral carbon atom causes confusion in the literature. Studies conducted on the short-term use of p-synephrine do not indicate its toxicity at low doses for healthy people. Further studies are needed to determine its long-term safety and possible interactions with other chemical compounds.

**Keywords:** p-synephrine, phytochemicals, Citrus species, dietary supplements

## SYNEPHRINE

Synephrine is a group of three isomeric substances differing in the position of the hydroxyl group connected with the aromatic ring in phenylethanolamine structure (Rossato et al., 2010; Stohs et al., 2011b). Depending on the place of substituent, there are three molecules: ortho-, meta-, and para-synephrine (see Figure 2). Due to the presence of a chiral carbon atom to which a hydroxyl group is attached in the aliphatic chain, it is possible to have two enantiomers: d- and l- for each of the 3 described compounds. By such a large number of possible isomers, 6 compounds are included in the synephrine group (Allison et al., 2005; Rossato et al., 2010). Another name for this compound is sympathol (respectively p-sympathol, etc.) (Bergmann and Sulzbacher, 1951). m-l-Synephrine is also known as a phenylephrine (Stohs and Preuss 2012). Phenylephrine has been confused in the literature with p-synephrine. Therefore, it is worthwhile to ensure which isomer was used (Bouchard et al., 2004; Nasir et al., 2004). The d- isomer is dextrorotatory and corresponds to the (S) configuration, while the l- isomer is levorotary and has the (R) configuration (Midgley et al., 1989). Freebase l-p-synephrine melts at 162-164 °C with decomposition, the most accurate measurements by differential scanning calorimetry show a melting point of racemic p-synephrine at 199.8 °C (Stewart et al., 1964; Rosa et al., 2016). p-Synephrine hydrochloride melts at 150-152 °C (Bergmann and Sulzbacher, 1951). p-d-Synephrine crystallizes in the orthorhombic crystal system (Ianno et al., 2020).

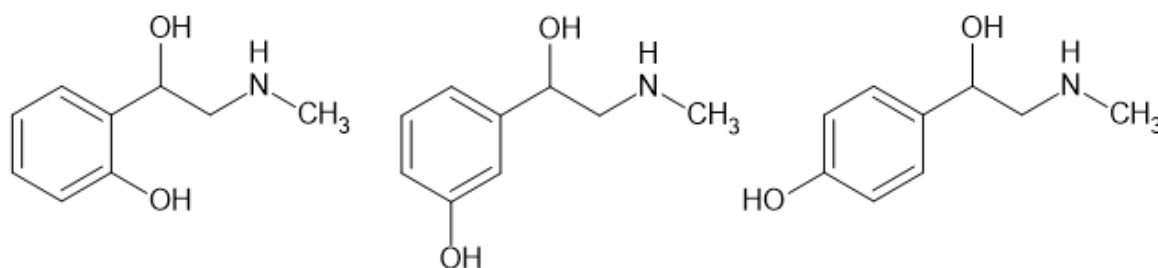
When exposed to UV light, p-synephrine can degrade. The main product of this process is 1-methyl-2,3-dihydro-1H-indole-3,6-diol. The formation of this product is attributed to the activity of the amine group. The resulting product in a study on human lymphocytes was characterized by genotoxicity and reduced cell viability (Malesuik et al., 2024).

p-Synephrine and bitter orange extract are ingredients in dietary supplements. They are advertised as weight loss remedies (Fugh-Berman and Myers, 2004; Rossato et al., 2011a). p-Synephrine use has been banned by sports organizations, including: The National Collegiate Athletic Association, Major League Baseball and The National Football League (Piattoly, 2022).

## SOURCES OF P-SYNEPHRINE

Plants are the most common source of p-synephrine. In addition, it occurs in animal tissues and cell lines.

p-Synephrine is the phytochemical in the *Citrus* species (*Rutaceae*). It is found in fruits and flowers of some citruses such as Bitter orange (*Citrus aurantium*), Pomelo (*Citrus grandis*), Cleopatra mandarin (*Citrus reshni*), Japanese mandarin (*Citrus unshiu*) and others (Wheaton and Stewart, 1969; Arbo et al., 2008; Dragull et al., 2008; Lin et al., 2023). It is assumed that only *para* enantiomer occurs in citruses (Stohs, 2013). However, the older scientific literature is uncertain about the natural occurrence of only one compound (Allison et al., 2005). The most commonly reported compound in the literature is para-l-synephrine, which is found in plants.

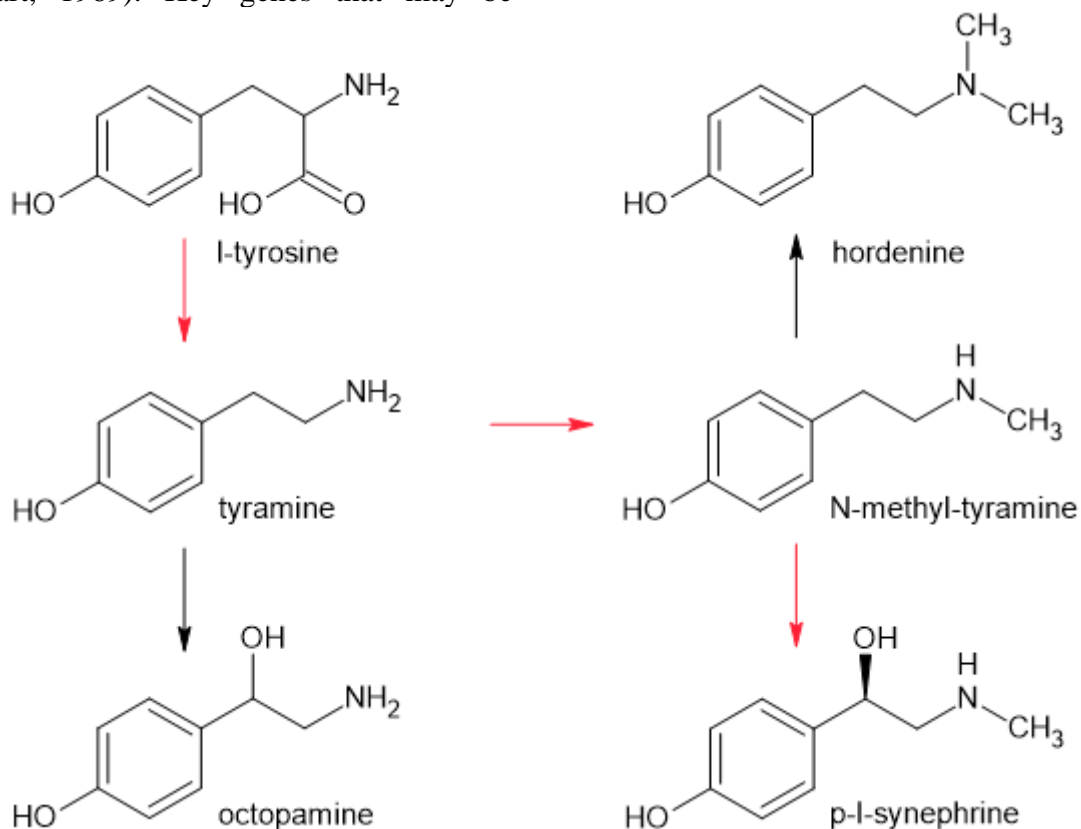


**Figure 2:** Chemical structures of o-, m- and p-synephrine

The biosynthesis reaction substrate is l-tyrosine (Bartley et al., 2010). However, small amounts of the d-isomer can be formed during extraction or processing fruits (Stohs and Preuss, 2012). Synephrine racemization is affected by factors such as pH and temperature. Therefore, extraction should be carried out under controlled conditions to prevent racemization. Previous literature reports of finding p-d-synephrine in plants may be due to poorly performed analyses or isomerization during fruit processing (Pellati et al., 2010). To prevent erroneous analytical results, enantioselective methods are available for the identification of synephrine isomers in biological samples (Pellati and Benvenuti, 2007). Wheaton and Stewart (1969) studied the biosynthesis of synephrine in *Citrus reshni*. Radio-traced studies with tyramine as a substrate showed a major pathway of phenolic amine synthesis (see Figure 3) (Wheaton and Stewart, 1969). Key genes that may be

responsible for biosynthesis have been identified (Zhong et al., 2024a).

A naturally biosynthesized compound is p-l-synephrine. Synthetic p-synephrine is a racemic mixture of l- and d-enantiomers (Stohs and Preuss, 2012). With this information, it is possible to determine whether the synephrine found in dietary supplements comes from plant sources (Koh et al., 2021). The molecule could also be used as a urinary biomarker for citrus consumption (Bader et al., 2017). It is also a potential biomarker of the authenticity of orange honey (Tette et al., 2017). p-Synephrine was identified in the urine collected from horses. Its source was the *Eragrostis* and *Lucerne* hay that the animals consumed (Brewer et al., 2022). p-Synephrine is sometimes called an elusive or trace amine. That is because the described molecule was found in the human body in plasma and platelet pellets in low quantities (D'Andrea et al.,



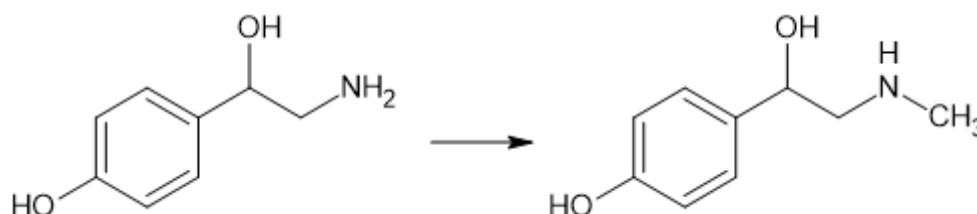
**Figure 3:** Biosynthesis of p-l-synephrine. The first step is decarboxylation, the second is methylation, and the last is hydroxylation. Tyramine could be hydroxylated to octopamine. N-methyl-tyramine could also be methylated to hordenine.

2003a, b; Arbo et al., 2008). p-Synephrine was detected in trace amounts in the urine of people who did not consume citrus in the last 12 hours, which may indicate the endogenous source of the discussed substance (Watson et al., 1990). Research on patients with migraines showed that the level of trace amines (including p-synephrine) was higher than in the control group (D'Andrea et al., 2006). Trace amines may act as neurotransmitters but p-synephrine's physiological role in the brain has not been understood (Arbo et al., 2008).

Levels of p-synephrine in Wistar rats were measured while studying the effects of dolutegravir on the trace amine profile (Henning et al., 2024). Dolutegravir is an antiviral drug and an HIV integrase inhibitor. It is also proposed as an anti-tumor drug (Hou et al., 2024). Synephrine was found in the urine of dolutegravir-treated rats as well as in the control group. In the dolutegravir-treated group, the concentration of synephrine in urine was slightly lower but still statistically significant (Henning et al., 2024). p- and m-Synephrine were also detected in the Caco-2 immortalized cell line (human colorectal adenocarcinoma) and cardiomyocytes collected from an adult rat (Rossato et al., 2010). Determinable amounts of p-synephrine indicate its endogenous source. Unfortunately, there have been no studies on its biosynthesis in the human body. It is believed to be formed by methylation of p-octopamine by phenylethanolamine N-methyltransferase (PNMT) (see Figure 4) (Lindemann and Hoener, 2005).

## PHARMACOLOGICAL ACTIVITY

Synephrine is a similar molecule to endogenous amines like epinephrine or norepinephrine. p-Synephrine interacts mainly with alpha ( $\alpha$ ) and beta ( $\beta$ ) adrenergic receptors. Localization of the hydroxyl group affects the binding strength of the substance to the  $\alpha$  and  $\beta$  receptors (Stohs et al., 2011b). It also shows an affinity for 5-HT<sub>1D</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>6</sub> receptors, trace amine-associated receptor 1 (TAAR1) and Neuromedin U2 receptor (NMU2R) (Wainscott et al., 2007; Hibino et al., 2009; Zheng et al., 2014; Koh et al., 2019; Wang et al., 2025). However, attention should be paid to the impermeability of the blood-brain barrier to p-synephrine. This property was verified using the SwissADME online tool (<http://www.swissadme.ch/index.php>, accessed on 23 January 2025) (Daina et al., 2017). The poor permeability of the test compound to the brain could limit the concentration of the described compound in the cerebrospinal fluid. This will result in marginal effects on receptors located in the brain. It should be remembered that in some diseases the blood-brain barrier can increase its permeability, resulting in greater penetration of certain substances into the brain (Dong, 2018). However, a study on mice showed that p-synephrine can cross the blood-brain barrier (Wang et al., 2025). This contradicts the *in silico* simulation. Further studies are needed to see if the described compound can cross this barrier in humans. Table 1 summarizes the effects of synephrine on individual receptors. Adrenergic receptors are distributed throughout the human body. Among other things, they are responsible for stress response, regulation of heart rate, blood



**Figure 4:** Possible pathway for p-synephrine biosynthesis in the human body from p-octopamine by PNMT

**Table 1:** The effect of p-syneprine on individual receptors

Molecular target	Function	Cell line/organ	Ki	50 % of the maximum possible effect (EC <sub>50</sub> )	Reference	The role of a particular receptor in the human body
$\alpha_{1A}$	partial agonist	HEK293 cell line	78,0 $\mu$ M	4 $\mu$ M	Ma et al., 2010b	It plays a role in cognitive processes, regulates blood pressure, glycolysis, cellular glucose uptake and fatty acid oxidation (Perez 2021)
$\alpha_{2A}$	antagonist	CHO cell line	36,7 $\mu$ M	N/A	Ma et al., 2010b	They are responsible for blood pressure and modulate inflammatory processes. They are also found in the central nervous system (Saunders and Limbird, 1999; Hering et al., 2020)
$\alpha_{2C}$	antagonist	CHO cell line	24,4 $\mu$ M	N/A	Ma et al., 2010b	
$\beta_1/\beta_2/\beta_3$	partial agonist	human induced pluripotent stem cell-derived cardiomyocytes	N/A	N/A	Yuan et al., 2024	They regulate blood pressure, heart rate, among other things. The $B_3$ receptor is also responsible for modulating lipolysis (Wachter and Gilbert, 2012; Samanta et al., 2024)
5-HT <sub>1D</sub>	agonist	rat aorta	N/A	N/A	Hibino et al., 2009	It occurs in small amounts in the central nervous system. It is responsible for constricting smooth muscles (Hoyer, 2019; Tanveer et al., 2024)
5-HT <sub>2A</sub>	agonist	rat aorta	N/A	N/A	Hibino et al., 2009	In the vascular system, it is responsible for modulating inflammation, wound healing and vasoconstriction. In the brain, it is responsible for memory and learning, the formation of hallucinations and other mental disorders (Zhang and Stackman, 2015; Tanveer et al., 2024)
5-HT <sub>6</sub>	antagonist	mouse mPFC and HMC-3 cell line	N/A	N/A	Wang et al., 2025	Receptors responsible for cognitive function, memory and mood regulation are present in the brain and are likely linked to eating behavior (Karila et al., 2015).
TAAR1	agonist	cloned human TAAR1 coexpressed in the AV12-664 cell line, Porcine coronary mesenteric artery	N/A	23,700 $\pm$ 6100 nM	Wainscott et al., 2007; Koh et al., 2019	This receptor regulates glucose levels, body weight, gastrointestinal hormone release, and influences food intake. It also regulates the reward system, cognitive processes and mood states, as well as the response of the glutamatergic, dopaminergic and serotonergic systems (Berry et al., 2017; Rutigliano et al., 2018)
NMU2R	agonist	HEK293 cell line	N/A	6,604 $\mu$ M	Zheng et al., 2014	The receptor regulates food intake and energy expenditure, a potential target in obesity therapy (Ma et al., 2014)

pressure and metabolic rate. They are stimulated by catecholamines such as adrenaline and norepinephrine. There are 9 receptors of these types in humans. Receptors of the adrenergic system can be divided into 3 groups:  $\alpha_1$ ,  $\alpha_2$  and  $\beta$ . Each group is divided into 3 subtypes (Wu et al., 2021; Xanthopoulos et al., 2021; Kraboth and Kalman, 2023). p-Synephrine acts on  $\alpha_{1A}$ ,  $\alpha_{2B}$ ,  $\alpha_{2C}$  and  $\beta_1$ ,  $\beta_2$ ,  $\beta_3$  receptors (Carpéné et al., 1999; Stohs et al., 2011b; Yuan et al., 2024).

### *In vitro studies*

Research on the human embryonic kidney (HEK293) cell line showed that p-synephrine is a partial agonist of the  $\alpha_{1A}$  adrenergic receptor. Maximal response to the receptor was given at a concentration of 100  $\mu\text{M}$ . A study on the Chinese ovary hamster (CHO) cell line showed an antagonistic effect on  $\alpha_{2B}$  and  $\alpha_{2C}$  receptors (Ma et al., 2010a).

The risk of inducing arrhythmias by p-synephrine was studied on human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) and freshly isolated rat cardiomyocytes. The study showed that the risk of inducing arrhythmias by p-synephrine through ingestion of doses used in dietary supplements is low. The risk of arrhythmia increases at concentrations higher than 200  $\mu\text{M}$ . An attempt to reverse changes in cardiomyocyte contractility was carried out using blockers selectively targeting  $\beta_1$ ,  $\beta_2$  and  $\beta_3$  receptors.  $\beta_1$  blockers almost completely reversed the changes induced by p-synephrine, indicating the affinity of the test compound mainly toward these receptors. In addition, the study showed that p-synephrine is more reactive towards human cardiomyocytes than rat cardiomyocytes (Yuan et al., 2024).

p-Synephrine is a highly potent agonist of NMU2R (Zheng et al., 2014). Central administration of neuromedin U is known to inhibit appetite by affecting NMU2R. Other molecules that interact with NMU2R can also regulate appetite (Bhattacharyya et al., 2004). This may explain the use of p-synephrine during weight loss (Zheng et al., 2014).

p-Synephrine is an antagonist of TAAR1, but its affinity is very low (Wainscott et al., 2007). Research on the effects of p-synephrine on TAAR1 is scarce, but the latest results indicate that p-synephrine may affect other TAAR receptor subtypes (Koh et al., 2019). In humans TAAR1 plays a role in regulation of the reward system, cognitive processes and mood regulation (Nair et al., 2022).

A study on mitochondria in the rat brain showed that synephrine can be metabolized by monoamine oxidase (MAO) types A and B. MAO type A showed higher activity (Suzuki et al., 1979).

p-Synephrine is transported by OCT1 and OCT3. In rat cardiomyocytes, it did not reduce GSH levels compared to m-synephrine, which generated more ROS. p-Synephrine penetrated cells in greater amounts than m-synephrine (Rossato et al., 2011b).

A study on rat skeletal myoblasts (L6) showed no cytotoxicity of p-synephrine after 24 hours of incubation. A concentration of p-synephrine in the medium higher than 25  $\mu\text{M}$  was shown to increase glucose consumption by cells. This is followed by increased lactic acid production. The study also showed that the tested compound increased the amount of the glucose transporter Glut4 after 2 hours incubation (Hong et al., 2012). Another study on rat hepatoma cells (H4IIE) tested how p-synephrine affects glucose profusion by cells. Adding p-synephrine to glucose-free medium at concentrations of 1; 5; 25; 100  $\mu\text{M}$  reduces glucose production by cells 24 hours after administration. Incubation of cells for 3 days in a p-synephrine-containing medium showed no cytotoxicity. It was tested whether inhibition of alpha and beta receptors could affect the aforementioned effects of the tested substance. The results indicate that p-synephrine suppresses glucose production by a different mechanism than interaction with the adrenergic system. This study also found that p-synephrine reduces glucose production by affecting serine/threonine kinase other than kinases A, C and G. In addition to this, the test

compound was found to have little effect on the lipid profile of cells (Cui et al., 2015).

A study on RAW267.7 macrophage mouse cell line showed the anti-inflammatory activity of p-synephrine. Cells were stimulated with lipopolysaccharide (LPS). p-Synephrine inhibits p38 MAPK and NF- $\kappa$ B pathways. Research on LPS-induced systemic inflammatory response syndrome (SIRS) mouse model revealed that p-synephrine given orally decreased proinflammatory cytokine levels in the serum. It was also connected with a higher survival rate of SIBS mice (Ishida et al., 2022). Another study on NF- $\kappa$ B and MAPK pathways was prepared on a mouse model of diabetes induced by alloxan injection. Administration of p-synephrine reduced the level of free radicals, increased glutathione level in the serum, improved glucose tolerance and reduced tissue insulin resistance. p-Synephrine also decreased inflammation in renal tissue; this activity could be caused by the regulation gene expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin 6 and interleukin 1 $\beta$ . The anti-inflammatory effects are likely connected with the regulation of MAPK and NF- $\kappa$ B pathways caused by synephrine (Wang et al., 2023). An *in vivo* study in a mouse model of acute lung injury induced by LPS administration, confirmed the anti-inflammatory properties of p-synephrine (5 and 10 mg/kg body weight, intraperitoneally before LPS administration). In this study, p-synephrine decreased TNF- $\alpha$  and IL-6, and increased IL-10. In the p-synephrine-treated group, lower amounts of the reactive oxygen species (ROS) in the lung tissue were measured, tissue edema and histopathological changes were also less significant. In addition, p-synephrine inhibited NF- $\kappa$ B phosphorylation (Wu et al., 2014).

p-Synephrine shows anti-adipogenic activity on 3T3-L1 cell line. This effect is due to regulation of the Akt pathway and suppression of adipogenesis-related proteins (Guo et al., 2019).

Research on the effects of p-synephrine on cancer is lacking. It has been shown that p-synephrine inhibits the proliferation, migra-

tion, colony formation and invasion capacity of esophageal squamous cell carcinoma (ESCC). Synephrine can downregulate galactin-3 expression by inactivating the AKT and ERK pathways. The sensitivity of cancer cells to 5-fluorouracil was also increased. An *in vivo* study in nude mice confirmed the anti-tumor effect of p-synephrine on ESCC tumor xenografts at doses of 20 mg/kg of animal body weight (Xu et al., 2018). p-Synephrine can bind to DNA through hydrophobic interactions. In lung cancer cells (H460), p-synephrine reduced their viability due to increased expression of Bax and p53 proteins. A decrease in PI3K, AKT and mTOR mRNA was also observed. This indicates a reduction in cancer cell proliferation through the interaction of the compound with the PI3K/AKT/mTOR pathway (Taheri et al., 2022).

The largest study on how p-synephrine alters gene expression was published in 2020. Tests were conducted on a Caco-2 cell line and human stomach mucosa cells (MNP01). p-Synephrine at concentrations of 2-200  $\mu$ M had no cytotoxic or mutagenic effects on both cell lines. The 24-hour incubation increased the amount of ROS in both cell lines, while it also increased the amount of GSH. This correlation may explain the lack of cytotoxicity. In addition, p-synephrine alters gene expression in the cells tested. In MNP01 cells, it upregulated the expression of ADCY3, MAPK1, JUN and AKT1, while it downregulated the expression of TNF gene. In the Caco-2 cell line, it upregulated the expression of MAPK1, GNAS, JUN, RELA, AKT1, PRKACA, PRKAR2A genes. Genes such as JUN and AKT1 are associated with proliferation, while RELA and TNF are associated with inflammation (Ribeiro et al., 2021).

A study on the 3T3 cell line showed that administration of p-synephrine inhibited interleukin-4 (IL-4) induced eotaxin-1 production. In contrast, it did not inhibit TNF- $\alpha$ -induced eotaxin-1 secretion. This indicates a specific inhibition of eotaxin-1 secretion caused by IL-4. The inhibition of eotaxin-1 secretion was caused by the inhibition of STAT6 phosphorylation by p-synephrine in

the JAK/STAT signaling pathway (Roh et al., 2014).

### **Studies in humans**

A study of tritium-labeled p-syneprine showed its pharmacokinetics and metabolism in humans. After oral administration, the highest plasma concentration was reached after 1-2 hours. The biological half-life was about 2 hours. With intravenous and oral administration, about 80 % of the radiation was recorded in urine. Two thirds of the tritium in urine was in p-hydroxymandelic acid (Hengstmann and Aulepp, 1978).

The study on 13 athletes showed no change in sports performance such as a squat jump, a countermovement jump, a 15-second repeated jump test, followed by 60-meter and 100-meter sprint contests. The subjects were given 3mg of p-syneprine per kilogram of body weight. After 45 minutes, sports tests were conducted. No side effects were found in the test subjects during or after the competition (Gutiérrez-Hellín et al., 2016). Another study using the same dosage showed an increase in the rate of fat oxidation, while the rate of carbohydrate oxidation during low-to-moderate intensity exercise was reduced. The increase in fat oxidation rate at the same exercise intensity and heart rate between the placebo group and the study group indicates an increased utilization of 7 grams of fat (Gutiérrez-Hellín and Del Coso, 2016).

A study of fifteen professional cyclists showed that administration of 3 mg per kg of body weight of p-syneprine resulted in an increase in the rate of fat oxidation compared to placebo. However, it had no effect on energy expenditure or heart rate (Gutiérrez-Hellín et al., 2021). Another study conducted by the same research team showed contradictory results. A test conducted on a group of 18 women who engaged in regular physical activity showed no change in the rate of fat oxidation. The dosage of p-syneprine remained the same. The only noticeable change was an increased eardrum temperature at rest. Heart rate also remained unchanged. The researchers suggested the gender of the subjects as a

possible explanation for the difference in the results (Gutiérrez-Hellín et al., 2022).

The effects of p-syneprine alone and in combination with bioflavonoids on self-esteem, blood pressure, heart rate and basal metabolism were studied on a group of 50 people. Administration of 50 mg of the pure compound or a mixture with naringin and hesperidin did not change resting heart rate, blood pressure or self-esteem. However, resting metabolism rate increased (Stohs et al., 2011a).

A non-obvious potential use for p-syneprine is as an ingredient in scalp rubs to reduce hair loss during hair styling. Many women experience hair loss during activities such as shampooing and brushing. Inside each hair follicle is an arrector pili muscle. These muscles are responsible for the piloerection commonly referred to as "goosebumps." Piloerection can be stimulated by mechanical, thermal or pharmacological stimuli. The pharmacological stimulus can be a response to the binding of catecholamines to the  $\alpha_1$  adrenergic receptor. During piloerection, a much greater force must be applied to pull out the hair. The study involved applying a preparation containing synephrine, which is a selective  $\alpha_1$  agonist, to the skin. The results showed that the application of a 10 % synephrine solution reduced the amount of hair loss during piloerection and increased the force needed to pull the hair out (McCoy et al., 2018).

### **Other studies**

The described compound has a weak affinity for 5-hydroxytryptamine (5-HT) receptors. A study conducted on the rat aorta has shown that p-syneprine, by acting on  $\alpha_1$ , 5-HT<sub>1D</sub> and 5-HT<sub>2A</sub> receptors, induces aortic constriction. The compound was found to have no effect on the 5-HT<sub>1B</sub> receptor (Hibino et al., 2009). Another study confirmed the induction of thoracic rat aortic contraction by p-syneprine (Kim et al., 2019).

p-Syneprine was tested on a mouse model of chronic social stress and on human microglia (HMC-3 cell line). It was shown that the tested compound reduced depressive



behavior in mice. In microglia, it promoted a change in cell phenotype from pro-inflammatory (M1) to anti-inflammatory (M2). Affinity for the 5-HT<sub>6</sub> receptor was proposed as the mechanism of action. Confirmation of p-syneprine's interaction with this receptor was obtained by Cellular Thermal Shift Assay (CETSA), molecular docking and coimmunoprecipitation. Binding of p-syneprine to the 5-HT<sub>6</sub> receptor inhibited interaction with the FYN protein, reduced activation of the ERK1/2 pathway which reduced the neuroinflammatory response and had an anti-depressive effect on mice (Wang et al., 2025).

In a mouse model, racemic p-syneprine was found to have antidepressant effects in a forced swimming and tail-hanging test. Preliminary results indicated an effect on the  $\alpha_1$  receptors. Another study on enantiomers of p-syneprine showed that both compounds effectively inhibit norepinephrine reuptake and stimulate norepinephrine action in cerebral cortex. d-p-Syneprine showed stronger reuptake inhibition. In the tail suspension test, only d-p-syneprine proved effective. This contrasts the fact that l-p-syneprine interacts more strongly with the  $\alpha_1$  receptors. It indicates that this enantiomer acts through a pathway other than interacting with the  $\alpha_1$  receptors. It is noteworthy that administration of d-p-syneprine in doses higher than 10 mg/kg lost its effectiveness in the tail suspension test. It is also surprising that p-syneprine crossed the brain-blood barrier of mice. Repeated administration of d-p-syneprine did not induce the tolerance effect. Besides, administration of d-p-syneprine to mice at a dose of 300 mg/kg did not cause any acute toxic effects (Song et al., 1996; Kim et al., 2001). As early as 1965, it was reported that racemic p-syneprine inhibits norepinephrine reuptake (Borgen and Iversen, 1965).

The effect of p-syneprine was examined on a dissected Wistar rat liver connected to a liver perfusion apparatus. The device enabled a controlled flow of a buffer through the organ. Administration of the tested compound resulted in higher hepatic lipase activity and increased excretion of free lipids by the liver.

The study showed that p-syneprine increases lipolysis (Silva-Pereira et al., 2017). Other studies on perfused rat livers have shown increases in glycolysis, glycogenolysis, and oxygen consumption. The proposed explanation for this effect is based on the impact of p-syneprine on adrenergic receptors (Peixoto et al., 2012; De Oliveira et al., 2014). A mouse study showed that feeding citrus p-syneprine to mice on a high-fat diet slowed adipose tissue proliferation and reduced the amount of mRNA for pro-inflammatory factors in perinephric adipose tissue. Surprisingly, administration of p-syneprine did not change the amount of serum lipids in a statistically significant way compared to the control group (Bai et al., 2024).

In the literature, information on p-syneprine-drug interactions are scarce. An *in silico* study testing the possibility of an interaction between metformin and p-syneprine has been reported in the literature. Metformin is a drug used to treat type 2 diabetes, and a theoretical study showed that a non-covalent bond could be formed including the two compounds between an amino group and a hydroxyl group. It is possible that two conformers could be formed, one of which showed high bioavailability. The described study is an attempt to develop a more effective diabetes drug with a lower dosage (Prince Makarios Paul et al., 2024). A different study in rats and rabbits looked at interactions with another diabetes drug, gliclazide. Healthy and diabetic animals were tested. A single administration of p-syneprine did not alter the pharmacokinetics and pharmacodynamics of gliclazide. Only repeated administration changed the pharmacodynamics of the drug - there was an increase in the reduction of glycemia in healthy and diseased rats and in healthy rabbits after administration of gliclazide. The observed change, according to the researchers, may be caused by the agonist effect of p-syneprine on  $\beta_3$  receptors (Vatsavai and Kilari, 2018).

An unusual use of p-syneprine, is as a scavenger of toxic aldehydes such as acrolein and glyoxal. The study showed that the

addition of p-synephrine to heat-treated foods allowed p-synephrine to bind acrolein. This effect also occurred *in vivo* in mouse studies for acrolein and glyoxal. This property suggests that the described substance may be a good food additive scavenging the mentioned two aldehydes (Jia et al., 2023; Liang et al., 2024a, b; Zhong et al., 2024b).

## STUDIES ABOUT TOXICITY AND SIDE EFFECTS OF P-SYNEPHRINE

There are many articles about the safety of synephrines as a group of substances. Table 2 summarizes the selected toxicity studies and their results.

### *Studies in experimental animals*

Animal studies mainly focus on the activity of the described compound. The toxicity itself is often a side topic and poorly discussed.

In a study on male mice, animals were administered bitter orange extract by oral gavage. The animal groups studied had 9-10 animals each. They were given the extract at 400, 2000 and 4000 mg/kg and p-synephrine at 30 and 300 mg/kg. The p-synephrine content of the extract was confirmed by a previously validated HPLC/UV method. The study lasted for 28 days, during which no overt signs of toxicity, morbidity, or mortality were observed. The increase in body weight in p-synephrine-treated animals was compared to the other groups. Catalase activity increased, while the amount of malondialdehyde decreased and the amount of glutathione increased. Other markers of oxidative stress were normal (Arbo et al., 2009).

The main limitations of this animal toxicity study are its duration, the testing of males only, and the possibility of different results in animals and humans. Side effects may appear after a longer period of time or due to interactions with other drugs. Teratogenicity and possible effects on future generations will also go unnoticed in such a short study.

### *In vitro studies*

Research on the cell line Caco-2 (immortalized human colorectal carcinoma) and freshly isolated cardiomyocytes from an adult rat showed that 3 hours of incubation in 1 mM or 500  $\mu$ M solutions of p- and m-isomers did not result in visible cytotoxicity (Rossato et al., 2010).

Research on human hepatocarcinoma cells (HepG2) showed that p-synephrine and caffeine alone do not reduce cell survival. Only simultaneous administration of both substances increased the percentage of dead cells. The combination of p-synephrine and caffeine increased the expression of genes related to apoptosis (BCL-2 and CASP9) and DNA repair (XPC), as well as decreased the expression of cell cycle control genes (CDKN1A). It was noted that the same relationship occurs for the amount of double-stranded DNA damage in cells (Leão et al., 2021). Another study on HepG2 cells confirmed the lack of cytotoxicity even at higher concentrations of p-synephrine. It was also shown that 6 hours incubation of cells with the test substance increased the amount of ROS. Associated with this was a cellular response involving an increase in glutathione and activation of other mechanisms to eliminate ROS. p-Synephrine did not alter the expression of genes associated with DNA damage response (ATM, ATR, CHEK1, CHEK2, TP53, SIRT1), suggesting that cellular defense mechanisms were sufficient to prevent intracellular damage (Ribeiro et al., 2019).

It should be noted that studies on cell lines do not reflect the effects of a particular compound on the whole organism. A drug can also be toxic to only a selected organ.

### *Studies in humans*

Two human studies conducted by Gutiérrez-Hellín et al. showed no side effects after administration of p-synephrine at a dose of 3 mg per kg of body weight during sports activities (Gutiérrez-Hellín et al., 2021, 2022). During the use of the supplement containing p-synephrine, the only possible side effect described by the authors was the possibility of

pupil dilation after the liquid entered the eyes (McCoy et al., 2018). Shara et al., study describing cardiovascular safety after oral administration of 49 mg of synephrine to 18 patients showed only a slight decrease in diastolic blood pressure (4.5 mmHg) 60 minutes after drug administration. Besides that, no other changes in heart rate, blood pressure, electrocardiograms or blood cell counts were noted (Shara et al., 2016).

Bui et al., described the effects of a single administration of 900 mg of bitter orange extract standardized to 6 % synephrine. Blood pressure increased, with systolic peaking at  $7,3 \pm 4,6$  mm Hg, diastolic at  $2,6 \pm 3,8$  mm Hg, and a heart rate change of  $4,2 \pm 4,5$  beats/min. However, the values were not large. The researchers noted that a limitation of their study was that it referred only to healthy subjects. In other groups of people such as the elderly, the sick or the obese, the results may be different (Bui et al., 2006).

The study on 18 healthy volunteers showed no changes in corrected QT interval and blood pressure compared to placebo. The subjects were given 450 mg of bitter orange extract standardized to 27 mg of m- and p-synephrine. Measurements were taken at 1, 3, 5 and 8 hours after administration (Min et al., 2005). Another study, conducted on 16 people for 15 days, consisted of administering 49 mg of p-synephrine daily and checking cardiovascular and hemodynamic parameters. No significant changes or adverse effects were registered (Shara et al., 2018).

The longest human study associated with p-synephrine lasted 60 days. The 75 subjects (15 men and 60 women between 27 and 76 years) were divided into three groups: a placebo group, a group receiving 49 mg p-synephrine in bitter orange extract, and a group receiving an extract with naringin and hesperidin. The subjects took two servings daily. No side effects were observed in this study. None of the participants reported adverse reactions. A limitation of the study was that patients were examined only before and after the end of taking p-synephrine. No examinations were conducted during the study, therefore, it

is not known what was happening to the subjects while actively taking p-synephrine. It is also not known whether the subjects took their medications appropriately, as plasma p-synephrine levels were not measured during the study (Kaats et al., 2013).

The study on 10 healthy adults (including three women) aged 20 to 31 years examined how oral administration of 21 mg of p-synephrine and 304 mg of caffeine would affect the human body during moderately intense exercise on a bicycle ergometer (for 30 minutes). The concentration of the tested compounds in the dietary supplement and the subjects' plasma was confirmed by LC/MS-MS. Plasma concentrations of p-synephrine and caffeine were measured for 12 hours, and vital signs, serum electrolytes, oxygen consumption and subjective sensation of exertion during exercise were monitored. No significant adverse events were reported. Diastolic blood pressure after exercise was higher after the supplement (mean 71.7 mmHg) than after placebo (63.0 mmHg). There were no significant differences in heart rate, systolic blood pressure or body temperature. Postprandial plasma glucose levels rose to 121.0 mg/dl after supplement administration and exercising compared to 103.7 mg/dl after placebo and exercising. An examination of subjective feelings showed that study participants rated exercise as less tiring after taking the supplement compared to the placebo group (Haller et al., 2008).

All human studies have been carried out on healthy and adult subjects. This makes it impossible to predict how p-synephrine will work on people who are sick, or belong to other age groups. Human studies have been conducted on groups with a female-to-male ratio other than 1:1. The effect of p-synephrine may vary by gender, this property has not been sufficiently studied.

### **Case reports (humans)**

A meta-analysis summarizing 18 articles involving a total of 341 study subjects included oral administration of p-synephrine at doses ranging from 6 to 214 mg. Both systolic

and diastolic blood pressure increased significantly after long-term p-synephrine use (6.37 mmHg for systolic pressure and 4.33 mmHg for diastolic pressure). Weight loss in the synephrine group was insignificant after long-term treatment and had no effect on body composition parameters. Based on the review, it was determined that the use of the substance described may elevate blood pressure and heart rate, which may increase the risk of stroke and heart attack in predisposed individuals (Koncz et al., 2022).

A review summarizing 35 people who experienced side effects that may be related to p-synephrine use indicates that the most common symptoms appeared on the cardiovascular side. Many patients took several supplements at once, making it impossible to pinpoint a single cause of symptoms. The review suggests that p-synephrine use may be associated with a higher risk of sudden cardiovascular-related illnesses such as heart attacks and arrhythmias. Limitations of the review include the small number of cases and uncertainty about the quality and purity of the dietary supplements that patients took (de Jonge et al., 2023).

Three selected cases of myocardial infarctions covered in the above review are discussed below. They all describe similar cases of people who took several substances at the same time.

One case is a 38-year-old man who suffered an ischemic stroke. The incident was preceded by numerous central nervous system symptoms such as double vision and dizziness. The patient was not in a stroke risk group. For a week before the incident, the patient had been taking a dietary supplement for weight loss. One tablet contained 6 mg of synephrine and 200 mg of caffeine alkaloids. The patient had been taking 1-2 tablets daily. At the end of the week-long hospitalization, the patient had almost completely recovered (Bouchard et al., 2005).

In 2002, a case of acute lateral-wall myocardial infarction in a 55-year-old woman was described. The incident coincided with the use of a dietary supplement containing bitter

orange. The patient's myocardial infarction began with standard clinical symptoms. The patient was hospitalized and received thrombolytic treatment. For the past year, she has been taking a dietary supplement for weight loss. The formula contained 300 mg of bitter orange and other additives such as green tea and guarana. The mentioned additives were a source of caffeine. The patient had no previous illnesses, and she had a history of smoking (Nykamp et al., 2004).

A 22-year-old man with no medical history was diagnosed with a ST-segment elevation myocardial infarction (STEMI). The symptoms of the infarction occurred during a basketball game, 2 hours after taking a dietary supplement. The patient had been taking two supplements over the past year, which included synephrine and bitter orange extract. Researchers linked the STEMI to the patient's intake of the supplements (Unnikrishnan et al., 2018).

Cases worthy of note are two patients admitted to the same emergency department within 48 hours. The first patient was a 28-year-old man with a history of HIV, mental illness and drug addiction. He was found unconscious on the street in a hyperthermic state. Among other things, cocaine, its metabolites and synephrine were detected in his serum. The synephrine concentration was 3010 ng/mL. The man was transferred to a rehabilitation center nearly three months after admission to the emergency department due to multiple complications. The second case involved a 24-year-old woman with a history of drug use. She was hospitalized after using crack and heroin. She had sinus tachycardia and developed hyperthermia while in the unit. Among other things, fentanyl and synephrine were detected in her serum. The synephrine concentration was 37700 ng/mL. Three days after the report, the patient left the hospital on her own request, with no neurological deficit. The cases described are noteworthy because of the huge concentrations of synephrine detected in patients. Most likely, synephrine was used as an adulterant in street drugs.

**Table 2:** Summary of the effect of p-synephrine in selected scientific papers

Model/Human studies	Time period	Synephrine dosage and administration	Main results	Reference
55 year old woman with a smoking history (case study)	1 year	A dietary supplement containing 300 mg of <i>Citrus auranticum</i> per day	Acute lateral-wall myocardial infarction	Nykamp et al., 2004
38 year old male without risk factors for stroke (case study)	1 week	1 or 2 capsules (6 mg p-synephrine and 200 mg of Kola nut extract containing caffeine alkaloids) per day	Ischemic stroke, almost completely recovered after one week of hospitalization	Bouchard et al., 2005
18 volunteers	8 hours	450 mg bitter orange extract standardized to 27 mg of m- or p-synephrine	No changes in rate corrected QTc and blood pressure	Min et al., 2005
15 volunteers	5 hours	900 mg bitter orange extract standardized to 54 mg p-synephrine	Slightly higher blood pressure	Bui et al., 2006
Mouse study	28 days	30 and 300 mg/kg by oral gavage per day	No signs of toxicity, changes in the levels of selected oxidative stress markers	Arbo et al., 2009
Caco-2 cell line, rat cardiomyocytes	3 hours	Incubation in 1 mM or 500 $\mu$ M p-synephrine in medium	Not cytotoxic, no visible differences in the viability of cardiomyocytes	Rossato et al., 2010
50 volunteers	75 minutes	50mg p-synephrine alone or with selected bioflavonoids	No side effects, no changes in subjects' self-esteem, increased resting metabolism rate	Stohs et al., 2011a
L6 cell line	24 hours	0; 25; 50; 100 $\mu$ M p-synephrine in medium	Lack of cytotoxicity, Increased glucose consumption after two hours of incubation	Hong et al., 2012
75 volunteers	60 days	49 mg p-synephrine standardized extract alone or mixed with chosen bioflavonoids twice a day	No side effects	Kaats et al., 2013
H4IIE cell line	3 days	1; 5; 25; 100 $\mu$ M p-synephrine in medium	Lack of cytotoxicity, reduced glucose production	Cui et al., 2015
13 sprinters	45 minutes	p-Synephrine 3 mg/kg	No changes in exercise performance, no side effects during and after exercises	Gutiérrez-Hellín et al., 2016
18 volunteers	1 hour	p-Synephrine 3 mg/kg	Elevated the rate of fat oxidation while decreasing the rate of carbohydrate oxidation during low-to-moderate exercise intensities	Gutiérrez-Hellín and Del Coso 2016
16 volunteers	15 days	49 mg of p-synephrine per day	No side effects	Shara et al., 2018

<b>Model/Human studies</b>	<b>Time period</b>	<b>Synephrine dosage and administration</b>	<b>Main results</b>	<b>Reference</b>
HepG2 cell line	24 hours	25-5000 $\mu$ M p-synephrine in medium	Lack of cytotoxicity	Ribeiro et al., 2019
MNP01 and Caco-2 cell lines	24 hours	2-200; 25-5000 $\mu$ M of p-synephrine in medium	Lack of cytotoxicity and mutagenicity, increased ROS levels, increased intracellular GSH levels, changed genes expression	Ribeiro et al., 2021
15 elite cyclists	1 hour	p-Synephrine 3 mg/kg	Increased the rate of fat oxidation during exercise	Gutiérrez-Hellín et al., 2021
HepG2 cell line	24 hours	0,03; 0,3; 3; 30 $\mu$ M p-synephrine in medium	Lack of cytotoxicity, concurrent administration with caffeine showed increased toxicity	Leão et al., 2021

Hyperthermia that proved difficult to control was most likely caused by synephrine. The amount of the substance in the plasma exceeded many times the amount consumed by people taking dietary supplements (Choe et al., 2023).

The main drawback of the case studies is the lack of information as to the exact purity of p-synephrine confirmed by an independent analytical lab. Information on the doses taken is also unclear. Often patients themselves do not know exactly what doses they have taken, taking dietary supplements irregularly. The unknown duration of exposure and additives make it very difficult to link p-synephrine to an increased risk of a particular disease.

## CONCLUSIONS

p-Synephrine is characterized by a broad spectrum of activity. It is advertised as a weight loss agent, which is supported by few scientific research papers. Studies on cell lines, animals, and humans do not indicate its toxicity at low doses. Therefore, short-term use of this compound in low doses is safe for healthy people. Adverse effects of p-synephrine have been reported in the literature; however, they relate to the use of large doses or the combination of this compound with other stimulants (such as caffeine). The described harmful effects may be due to diseases unrelated to p-synephrine use. Research on its long-term effects on human health is lacking. Because it is found in citrus fruit products, it is part of the diet for those who consume these fruits. It also plays a role in neuropharmacology, however, it has not been sufficiently studied. Due to the isomeric substitution of the hydroxyl group to the aromatic ring, there may be confusion in the literature. The presence of a chiral carbon atom means that inaccuracies regarding the single enantiomer or racemate used are present in the studies. Available studies indicate that plant-derived p-synephrine is safe for healthy people in low doses with short-term use. Further studies are needed to thoroughly investigate the effects of this compound and its isomers.

## Methodology of the review

The manuscript was based on a conducted review of online databases of scientific articles such as PubMed, Embase, Scopus, Web of Science, and Google Scholar. The key search term used was ‘p-synephrine’. The relevance of the articles was determined by reviewing their abstracts. The focus was mainly on articles related to *in vitro* and *in vivo* studies. The manuscript includes articles published before 2025.

## Authors’ contributions

Conceptualization, MK, KB and AK; writing—original draft preparation, MK, KB and AK; writing—review and editing, MK, KB and AK; supervision, AK All authors have read and agreed to the published version of the manuscript.

## Competing interests

The authors declare that they have no conflict of interest.

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