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Pharmacologists work for a better medicine tomorrow

Artichoke (*Cynara scolymus* L.): a review of its health-promoting properties

Rethinking post-mortem tryptase: a critical analysis of its role in diagnosing anaphylactic deaths

A review of metabolic syndrome: diet, physical activity and natural remedies

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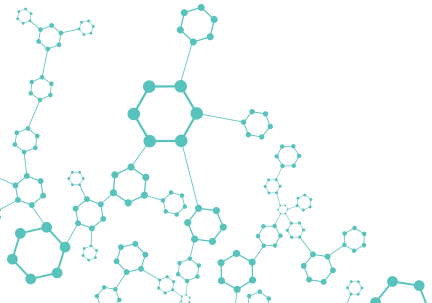

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PHARMACOLOGISTS WORK FOR A BETTER MEDICINE TOMORROW

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The title of this Editorial echoes that of the latest Italian Society of Pharmacology (Società Italiana di Farmacologia, SIF) meeting, held in beautiful Sorrento, Italy, in November 2024. Even a cursory look at the program (available online) testifies to the enormous amount of work that researchers are undertaking daily to contribute to the progress of medicine, therapy, and, in turn, human health. From RNA interference (1) to molecular biology (2), from the cardiovascular system (3, 4) to the central nervous system (5), from cancer therapy (6) to gut health (2), *etc.*, the field of pharmacology is thriving and can only get better in the future. Indeed, the word "pharmacology" now encompasses natural products (7, 8) and markers used in forensic medicine (9), basic mechanisms and clinical trials, computer science and informatics.

PharmAdvances is exactly that: *nomen-omen*. The continuous and unstoppable progress that scientific research is witnessing will certainly benefit future patients. Even though public health and preventive medicine should be at the forefront of maintaining human health, things can go wrong (as we know too well) and diseases might strike (10). This is why we need new and better drugs, as discussed at the SIF congress, via appropriate infrastructures, financial investments (often mistaken for vague expenditures), and hard work in the laboratories and in the wards. Despite the current world uncertainties, ravaging wars, financial instability, dramatic climate change, and the apparent inability of human beings to live together in peace and prosper, humanity is making big progress, and the future is always better than the present.

I encourage everyone to peruse the 42nd SIF meeting program (https://congresso2024.sifweb.org/programma-congresso) and find out how strong pharmacological research is becoming.

Everyone should contribute to the advancement of science, and PharmAdvances is waiting for your contributions to disseminate them worldwide.

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REVIEW

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Volume **6**, issue **1**, **2024: 7-24**

ARTICHOKE (*CYNARA SCOLYMUS* L.): A REVIEW OF ITS HEALTH-PROMOTING PROPERTIES

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SUMMARY

Cynara scolymus L., called artichoke or globe artichoke, is a perennial herbaceous plant cultivated worldwide. This plant is a common component of the Mediterranean diet and has been used as a remedy for health conditions since antiquity. The aim of this review is to find the health-promoting properties of artichoke, conducting a literature search in PubMed. The results show that 119 studies describe these effects, and 17 health benefits of artichoke are reported in the scientific literature. Antioxidant activity and effects on the liver and lipid profile are the main health-promoting properties of this plant. We found that artichoke also improves cardiovascular and gastrointestinal health and exerts anticancer, antimetabolic and antiobesity, prebiotic and probiotic, renoprotective and antidiabetic activities. Only one or two research articles reported the positive effects of this plant on the immune system, arthritis, photoaging, the reproductive system, the nervous system, fungal infections and periodontal diseases. The health benefits are mainly exerted by phenolics. In conclusion, this review shows the health-promoting properties of artichoke. The main beneficial effects are antioxidant activity and effects on lipid profile and the liver, which are mainly mediated by phenolics. The results of the scientific articles described in this review and the molecular mechanisms related to the health benefits of artichoke should be confirmed by future experimental studies.

Key words
Artichoke, Cynara scolymus L., antioxidant, hepatoprotective, lipid profile.

Impact statement
Artichoke (*Cynara scolymus* L.) has many health benefits, and the main properties are antioxidant activity and effects on the liver and lipid profile.

INTRODUCTION

Cynara scolymus L. is a plant species which belongs to the family *Asteraceae* (1). This perennial plant, commonly known as artichoke or globe artichoke, is grown worldwide. Artichoke is endemic to the Mediterranean region and has probably been tamed in southern Italy. The Arabs brought it to other parts of the Mediterranean in medieval times (2). Ancient populations did know artichoke for its nutritional and health-promoting properties (3). The scientific name comes from the Latin word '*cinis*' and the Greek word '*skolymos*', which mean 'ash' and 'cardoon', respectively (4).
Artichoke is an herbaceous plant that can reach about 1,80 meters in height. The flower head is globe-shaped with green and violet external bracts. The receptacle is located in the lower part of the artichoke head and the "choke" made up of bristles is found above it. Many blue-purple

Figure 1. **Artichoke**. A botanical illustration of artichoke. (*Cynara scolymus* by Adriana Morgante Giornetti).

flowers are arranged in the center of the head (**Figure 1**). Artichoke buds are cut before blooming and the edible part includes the receptacle and the inner bracts (5, 6). This plant is a common ingredient of the Mediterranean diet and is widely utilized for health purposes. Artichoke leaves are mainly used in infusions and extracts for their health-promoting properties (7, 8).

This plant contains minerals, vitamins, dietary fibers and bioactive compounds, which are responsible for its beneficial effects. Phenolics include: hydroxycinnamic acids, such as chlorogenic acid (**Figure 2**), caffeic acid and cynarine (**Figure 3**); anthocyanidins, such as cyanidin; flavones, such as apigenin and luteolin (**Figure 4**). Triterpenes and sesquiterpene lactones (*e.g.*, cynaropicrin) (**Figure 5**) are also found in artichoke. Finally, this plant contains inulin, which is a fiber with health-promoting properties (9-13).

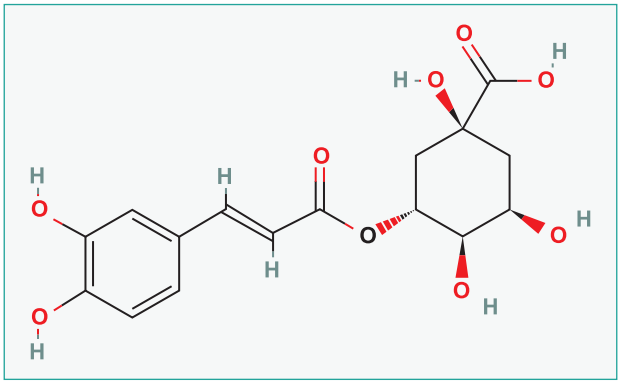

Figure 2. Chlorogenic acid. A chemical structure image of chlorogenic acid (Retrieved from: https://pubchem.ncbi.nlm.nih.gov/compound/1794427#section=2D-Structure. Accessed: Oct 30, 2024).

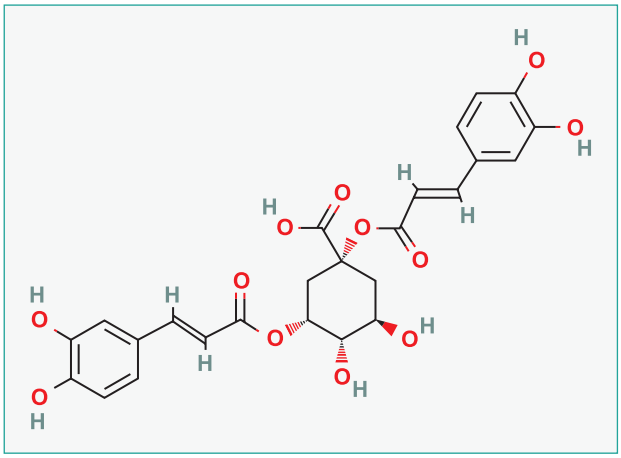

Figure 3. Cynarine. A chemical structure image of cynarine (Retrieved from: https://pubchem.ncbi.nlm.nih.gov/compound/5281769#section=2D-Structure. Accessed: Oct 30, 2024).

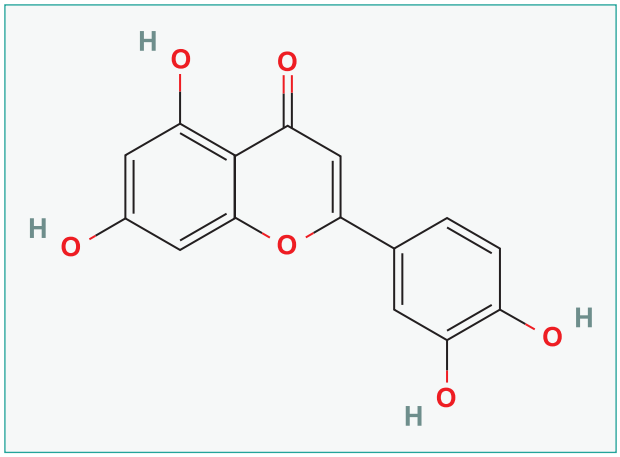

Figure 4. Luteolin. A chemical structure image of luteolin (Retrieved from: https://pubchem.ncbi.nlm.nih.gov/compound/5280445#section=2D-Structure. Accessed: Oct 30, 2024).

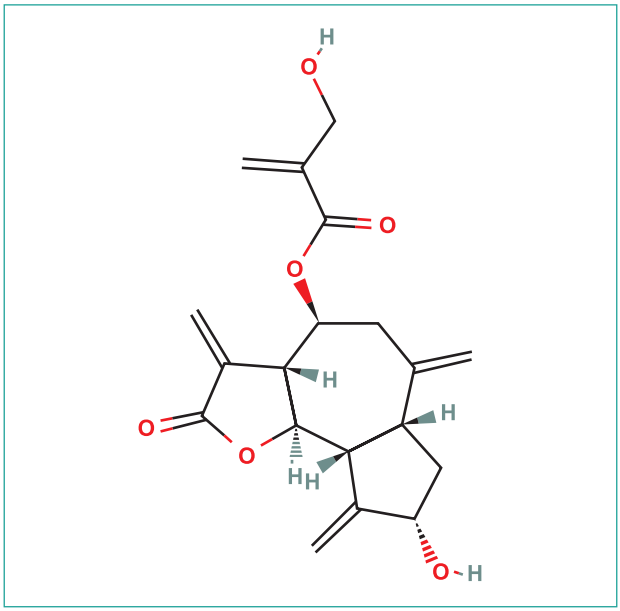

Figure 5. Cynaropicrin. A chemical structure image of cynaropicrin (Retrieved from: https://pubchem.ncbi.nlm.nih.gov/compound/119093#section=2D-Structure. Accessed: Oct 30, 2024).

In this review, we search scientific literature to identify the health benefits of artichoke. This plant has been used for treating health conditions since ancient times and is still largely utilized by healthcare and herbal practitioners. Research has focused on its properties and there is increasing interest in the different beneficial effects and the molecular mechanisms involved in these activities. Our work has great significance, as it includes the latest research findings on this topic.

METHODS

We investigated the beneficial effects of artichoke on human health, searching for scientific articles in the PubMed database (https://pubmed.ncbi.nlm.nih.gov/). The following keywords were used: 'artichoke', '*Cynara scolymus*', 'artichoke therapeutic effects', '*Cynara scolymus* therapeutic effects', 'artichoke properties', 'artichoke health benefits', 'artichoke health-promoting properties', 'artichoke phytotherapy', '*Cynara scolymus* phytotherapy', 'artichoke disease treatment' and '*Cynara scolymus* disease treatment'. The article types selected in PubMed were clinical trials, randomized controlled trials, books and documents. We included only previous studies relating to the topic of this review and written in English. We excluded reviews, systematic reviews, meta-analyses and articles which show only negative results or adverse effects of artichoke. We chose scientific studies through an initial screening by reading titles and abstracts. In a second moment, we read the whole text to find the proper scientific articles.

RESULTS AND DISCUSSION

The results of literature search indicate that 1374 articles are included in PubMed. We chose 119 studies after article screening and we identified 17 health-promoting properties of artichoke (**Table 1**).

Table 1. Health-promoting properties of artichoke. The table shows the beneficial properties of artichoke and the scientific articles which report these effects.

Health-promoting effects	References
Effects on the liver	Ahmadi *et al.*, 2019; Ben Salem *et al.*, 2017b; Ben Salem *et al.*, 2019; Celepli *et al.*, 2022a; Celepli *et al.*, 2022b; Colak *et al.*, 2016; Deng *et al.*, 2022; El-Boshy *et al.*, 2017; El Morsy and Kamel, 2015; Elsayed Elgarawany *et al.*, 2020; Frigerio *et al.*, 2021; Gebhardt, 1997; Gebhardt, 2001; Gebhardt, 2002a; Gebhardt, 2002b; Gebhardt and Fausel, 1997; Heidarian and Rafieian-Kopaei, 2013; Kirchhoff *et al.*, 1994; Küçükgergin *et al.*, 2010; Kurt *et al.*, 2014; Kwon *et al.*, 2018; Lee *et al.*, 2021b ; Liao *et al.*, 2021; Majnooni *et al.*, 2021; Mehmetçik *et al.*, 2008; Menghini *et al.*, 2010; Metwally *et al.*, 2011; Miccadei *et al.*, 2008; Nasef *et al.*, 2022; Panahi *et al.*, 2018; Qiang *et al.*, 2012; Rangboo *et al.*, 2016; Saénz Rodriguez *et al.*, 2002; Sharaf El-Deen *et al.*, 2017; Speroni *et al.*, 2003; Sümer *et al.*, 2020; Tang *et al.*, 2017; Wang *et al.*, 2021; Wauquier *et al.*, 2021

Effects on lipid profile	Ben Salem *et al.*, 2017b; Ben Salem *et al.*, 2019; Ben Salem *et al.*, 2022a; Bogavac-Stanojevic *et al.*, 2018; Bundy *et al.*, 2008; Deng *et al.*, 2022; Englisch *et al.*, 2000; Frigerio *et al.*, 2021; Gebhardt, 1998; Heidarian and Rafieian-Kopaei, 2013; Ibrahim *et al.*, 2022; Küçükgergin *et al.*, 2010; Küskü-Kiraz *et al.*, 2010; Kwon *et al.*, 2018; Liao *et al.*, 2021; Majnooni *et al.*, 2021; Panahi *et al.*, 2018; Qiang *et al.*, 2012; Qinna *et al.*, 2012; Rangboo *et al.*, 2016; Rondanelli *et al.*, 2013; Rondanelli *et al.*, 2014; Rondanelli *et al.*, 2019; Shimoda *et al.*, 2003; Tang *et al.*, 2017; Wauquier *et al.*, 2021
Effects on the cardiovascular system	Ben Salem *et al.*, 2022a; Bogavac-Stanojevic *et al.*, 2018; Crevar-Sakac *et al.*, 2016; Juzyszyn *et al.*, 2008; Küçükgergin *et al.*, 2010; Li *et al.*, 2004; Lupattelli *et al.*, 2004; Roghani-Dehkordi and Kamkhah, 2009; Wang *et al.*, 2021; Xia *et al.*, 2014; Zapolska-Downar *et al.*, 2002
Effects on the gastrointestinal system	Bundy *et al.*, 2004; Emendörfer *et al.*, 2005; Holtmann *et al.*, 2003; Ishida *et al.*, 2010; Marakis *et al.*, 2002; Nassar *et al.*, 2013; Sabater *et al.*, 2019; Verspohl *et al.*, 2008; Walker *et al.*, 2001
Antimetabolic and antiobesity activity	Ardalani *et al.*, 2020; Ben Salem *et al.*, 2019; Ben Salem *et al.*, 2022a; Ebrahimi-Mameghani *et al.*, 2018; Kwon *et al.*, 2018; Rezazadeh *et al.*, 2018a; Rezazadeh *et al.*, 2018b; Rondanelli *et al.*, 2014; Wauquier *et al.*, 2021
Anticancer activity	Abdel-Moneim *et al.*, 2021; Ding *et al.*, 2021; Islam *et al.*, 2021; Lepore *et al.*, 2019; Liu *et al.*, 2019; Menghini *et al.*, 2010; Metwally *et al.*, 2011; Miccadei *et al.*, 2008; Mileo *et al.*, 2012; Mileo *et al.*, 2015; Mileo *et al.*, 2020; Muti *et al.*, 2022; Pulito *et al.*, 2015; Villarini *et al.*, 2021; Yang *et al.*, 2022
Probiotic and prebiotic activities	Costabile *et al.*, 2010; Fissore *et al.*, 2015; López-Molina *et al.*, 2005; Riezzo *et al.*, 2012; Valerio *et al.*, 2010; Van den Abbeele *et al.*, 2020; Zeaiter *et al.*, 2019
Antioxidant activity	Abdel-Moneim *et al.*, 2021; Ahmadi *et al.*, 2019; Ben Salem *et al.*, 2017a; Ben Salem *et al.*, 2017b; Ben Salem *et al.*, 2019; Ben Salem *et al.*, 2022a; Ben Salem *et al.*, 2022b; Biel *et al.*, 2020; Bogavac-Stanojevic *et al.*, 2018; Brown and Rice-Evans, 1998; Carpentieri *et al.*, 2022; Celepli *et al.*, 2022a; Celepli *et al.*, 2022b; Cicek *et al.*, 2022; Colak *et al.*, 2016; Crevar-Sakac *et al.*, 2016; D'Antuono *et al.*, 2018; Deng *et al.*, 2022; Durazzo *et al.*, 2013; El-Boshy *et al.*, 2017; El Morsy and Kamel, 2015; Elsayed Elgarawany *et al.*, 2020; Gebhardt, 1997; Gebhardt and Fausel, 1997; Gurel *et al.*, 2007; Heidarian and Rafieian-Kopaei, 2013; Ibrahim *et al.*, 2022; Jiménez-Escrig *et al.*, 2003; Juzyszyn *et al.*, 2008; Khattab *et al.*, 2016; Kostić *et al.*, 2021; Küçükgergin *et al.*, 2010; Küskü-Kiraz *et al.*, 2010; Lee *et al.*, 2021a; Lee *et al.*, 2021b; Liao *et al.*, 2021; Lin *et al.*, 2022; Liu *et al.*, 2019; Magielse *et al.*, 2014; Matsumoto *et al.*, 2021; Mehmetçik *et al.*, 2008; Menghini *et al.*, 2010; Metwally *et al.*, 2011; Miccadei *et al.*, 2008; Mohammed *et al.*, 2020; Nasef *et al.*, 2022; Nassar *et al.*, 2013; Pérez-García *et al.*, 2000; Rezazadeh *et al.*, 2018a; Sarawek *et al.*, 2008; Skarpanska-Stejnborn *et al.*, 2008; Speroni *et al.*, 2003; Takei *et al.*, 2015; Tang *et al.*, 2017; Wang *et al.*, 2021; Xia *et al.*, 2014; Zapolska-Downar *et al.*, 2002
Antidiabetic effects	Ben Salem *et al.*, 2017b; Deng *et al.*, 2022; Ebrahimi-Mameghani *et al.*, 2018; Fantini *et al.*, 2011; Ibrahim et al., 2022; Kwon *et al.*, 2018; Rondanelli *et al.*, 2014
Antiarthritic effects	Masutani *et al.*, 2016; Wauquier *et al.*, 2021
Renoprotective activity	Ben Salem *et al.*, 2022b; El-Boshy *et al.*, 2017; Khattab *et al.*, 2016; Sümer *et al.*, 2020; Wang *et al.*, 2021
Neuroprotective effects	Cicek *et al.*, 2022; Ibrahim et al., 2022
Effects on the reproductive system	Gurel *et al.*, 2007; Mohammed *et al.*, 2020

Effects on the immune system	El-Boshy *et al.*, 2017; Hueza *et al.*, 2019
Antiphotoaging effects	Takei *et al.*, 2015; Tanaka *et al.*, 2013
Antifungal effects	Zhu *et al.*, 2005
Prevention of periodontal diseases	Hayata *et al.*, 2019

Effects on the liver

Several research studies examined the effects of artichoke consumption on the liver, performing *in vivo* and *in vitro* experiments. Two studies showed the beneficial effect of artichoke leaf extract (ALE) alone (14) or in combination with metformin or vitamin E (15) in individuals with non-alcoholic fatty liver disease (NAFLD). Artichoke extracts also improve NAFLD in rodents (16, 17). Rangboo and colleagues (18) showed that ALE exerts hepatoprotective activity in a sample of 60 individuals with non-alcoholic steatohepatitis (NASH), while Tang and colleagues (19) found that an artichoke extract has a beneficial effect on alcoholic liver disease (ALD) in mice. Previous studies demonstrated that ALE exerts hepatoprotective effects *in vivo* (20-35), *in vitro* (36) and *ex vivo* (37). Stem and receptacle extracts have this effect in rats (38) and an extract with high phenolic content exerts hepatoprotective and choleretic effects in rats (39). Previous scientific articles reported that artichoke has hepatoprotective effects in these laboratory animals (40-42). Qiang and colleagues (43) found that ALE increases bile acid secretion in hamsters. Artichoke extracts exert choleretic activity *in vivo* (44, 45) and *in vitro* (46). Previous studies demonstrated that these plant extracts have hepatoprotective (47-49) and anticholestatic (50, 51) effects *in vitro*, which are mainly exerted by phenolics. Gebhardt (52) showed that liver cholesterol synthesis can be inhibited by ALE *in vitro,* and flavones are the bioactive compounds mainly involved in this effect.

Effects on lipid profile

The effects of artichoke consumption on lipid profile are well documented in scientific literature. ALE intake alone (14) or in association with metformin or vitamin E (15) improves lipid profile in individuals with NAFLD. A study by Rangboo *et al.* (18) showed that ALE consumption is effective in lowering triglycerides, total cholesterol and low-density lipoprotein cholesterol (LDL-C) in a cohort of 60 individuals with NASH. Shimoda and colleagues (53) demonstrated that the beneficial effect of artichoke on lipid profile is exerted by sesquiterpenes. Another study by Bundy *et al.* (54) showed that ALE can be effective in reducing total cholesterol in individuals with hypercholesterolemia. Englisch and colleagues (55) demonstrated that ALE can lower LDL-C and total cholesterol in a cohort of 143 individuals with hyperlipoproteinemia. A previous study by Rondanelli *et al.* (56) found that ALE intake reduces total cholesterol and LDL-C and raises high-density lipoprotein cholesterol (HDL-C) in a sample of 92 patients with hypercholesterolemia, while other scientific articles reported that artichoke extracts can decrease triglycerides, total cholesterol and LDL-C and improve HDL-C in rats (16, 21). Rondanelli and colleagues (57) demonstrated that ALE improves HDL-C and lowers total cholesterol/HDL-C ratio in a cohort of 20 individuals with mild hypercholesterolemia. Another study found that consumption of an artichoke extract ameliorates lipid profile in a sample of 55 overweight individuals with impaired fasting glycemia (58). Two articles reported the beneficial effect of ALE on cholesterol homeostasis, performing *in vitro* (46) and *ex vivo* (37) experiments. Many research studies found the beneficial effect of artichoke extracts on lipid profile in rodents (19, 22, 28, 29, 31, 32, 43, 59, 60-63). A study by Gebhardt (64) showed that ALE is effective

in suppressing hepatic cholesterol synthesis in rats and luteolin is implicated in this activity.

Effects on the cardiovascular system

Artichoke intake may exert beneficial effects on the cardiovascular system. A previous study by Lupattelli *et al.* (65) found that artichoke leaf juice has beneficial effects on endothelial function in a sample of 28 individuals with hyperlipidemia, while Roghani-Dehkordi and Kamkhah (66) demonstrated that artichoke leaf juice is effective in reducing blood pressure in individuals with mild hypertension. Artichoke extracts exert protective effects on the cardiovascular system *in vivo* (29, 59, 60, 67) and *in vitro* (68, 69). A previous scientific article reported the health benefits of artichoke bud extract in a rat model of hypertension (42). Li and colleagues (70) found that ALE can improve expression and function of endothelial nitric oxide synthase (eNOS), performing *in vitro* and *ex vivo* experiments and flavones are involved in this activity. ALE can also inhibit the expression of inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells and the phytochemical compounds mainly implicated in this effect are cynarine and cyanidin (71).

Effects on the gastrointestinal system

The oral intake of artichoke can improve gastrointestinal health in humans and animal models. Previous studies demonstrated the beneficial effect of ALE on the gastrointestinal system in individuals with functional (72) and mild (73) dyspepsia. Other studies showed that ALE is effective in alleviating irritable bowel syndrome (IBS) symptoms in individuals with this condition (74, 75). Nassar and colleagues (76) found that an artichoke head extract can exert antiulcerogenic activity in rats. Cynaropicrin is the bioactive compound which may exert antispasmodic effects on the gastrointestinal tract of guinea pigs (77) and antigastritis activities in rats (78). Verspohl and colleagues (2008) demonstrated the beneficial effect of ALE on IBS in an experiment performed on the ileum of rats and a previous study found the anti-colitis activity of artichoke pectin in mice (80).

Antimetabolic and antiobesity activity

The beneficial effects of artichoke consumption on metabolic syndrome and obesity are described in recent research articles. ALE intake may be effective in ameliorating metabolic syndrome biomarkers (81-83). Ardalani and colleagues (84) found that ALE can reduce body mass index (BMI) in overweight individuals, while Wauquier and colleagues (37) demonstrated the protective effect of ALE on obesity and metabolic syndrome, performing an *ex vivo* study. A previous study showed the health benefits of an artichoke extract, studying a cohort of 55 overweight individuals with impaired fasting glycemia (58). Recent research articles demonstrated the antiobesity and antimetabolic syndrome activities of ALE in rodents (22, 31, 59).

Anticancer activity

The anticancer activity of artichoke is well reported in the scientific literature. A previous study showed the protective effect of an artichoke extract on pleural mesothelioma in a sample of 18 individuals with asbestos-related benign pleural disease (85). ALE exerts antitumor effect against malignant pleural mesothelioma *in vivo* and *in vitro* (86). Liu and colleagues (87) demonstrated the anticancer activity of cynaropicrin in HeLa cells. This bioactive compound found in artichoke may exert an inhibitory effect on thioredoxin reductase and promote oxidative stress, which leads to apoptosis. Previous studies showed the beneficial effects of this plant in a rat model of hepatocellular carcinoma (41) and the potential anticancer effects of artichoke extracts in human hepatocellular carcinoma (36, 49), uterine leiomyoma (88), breast cancer (89-91) and colon cancer (92) cells. Cynaropicrin may exert anticancer activity in anaplastic thyroid cancer (93) and lung carcinoma (94) cells. Yang and colleagues (95) showed the antitumor effects of this bioactive compound against neuro-

blastoma *in vivo* and *in vitro*. A study by Abdel-Moneim *et al.* (96) found the beneficial effect of artichoke extracts on lung cancer in rats, which is exerted mainly through antioxidant, proapoptotic and antiproliferative activities.

Probiotic and prebiotic activities

Artichoke may exert probiotic and prebiotic activities, as demonstrated by human and *in vitro* studies. The oral intake of artichoke fortified with a probiotic (*i.e.*, *Lactobacillus paracasei*) can improve constipation in individuals with this condition (97, 98). Previous research studies reported the prebiotic activity of long-chain inulin from artichoke in a sample of 31 healthy individuals (99) and *in vitro* (100, 101). Fissore and colleagues (102) demonstrated that artichoke fibers *(i.e.*, inulin and pectin of low degree of methylation) have prebiotic effects *in vitro*. A study by Van den Abbeele *et al.* (103) showed that an artichoke extract exerts this activity *in vitro*.

Antioxidant activity

Artichoke is a source of bioactive compounds, and its antioxidant activity has been demonstrated in many research studies involving humans, animal models and *in vitro*. ALE intake exerts antioxidant activity in individuals with metabolic syndrome, lowering oxidized-LDL (ox-LDL) levels (82). Skarpanska-Stejnborn and colleagues (104) showed the antioxidant effect of ALE in a sample of 22 rowers during the training. The antioxidant activity of cynaropicrin from artichoke was demonstrated in HeLa cells (87) and human keratinocytes (105). Sesquiterpene lactones (106) or cynarine and cyanidin (71) from artichoke can inhibit the expression of iNOS *in vitro*. Many previous studies showed that artichoke extracts exert this activity in rodent models of different health conditions (16, 19-29, 32-34,40-42, 59-62, 67,76, 96, 107-112). Lee and colleagues (17) found the protective role of ALE against oxidative stress, performing experiments in NAFLD mice and HepG2 cells. Other studies showed the beneficial effect of artichoke extracts with high phenolic contents on oxidative stress (39, 113-115). Pérez-García and colleagues (116) demonstrated the antioxidant effect of ALE *in vitro*. This artichoke extract is effective in blocking reactive oxygen species (ROS) generation in human leukocytes and the phytochemicals mainly involved are luteolin, caffeic acid, cynarine and chlorogenic acid. Previous studies showed that artichoke extracts exert antioxidant activity *in vitro* (36, 47-49, 68, 69, 117). Sarawek and colleagues (118) found that luteolin from artichoke is effective in inhibiting xanthine oxidase (XO) *in vitro*. Two previous studies showed the antioxidant effects of these plant extracts, performing *in vivo* and *in vitro* experiments (119, 120). Artichoke seeds (121), rhizome (122), buds (123) and pollen (124) exert antioxidant activity and phenolics are mainly involved in this beneficial effect.

Antidiabetic effects

The consumption of artichoke may have antidiabetic effects, as demonstrated by research studies on humans and animal models. Rondanelli and colleagues (58) found the beneficial effect of an artichoke extract on glucose metabolism in a sample of 55 overweight individuals with impaired fasting glycemia. Artichoke extracts are effective in improving insulin resistance in individuals with metabolic syndrome (81) and rodents (16, 31, 61). Ben Salem and colleagues (21) found the antihyperglycemic activity of ALE in diabetic rats. The hypoglycemic activity of an artichoke flower head extract was demonstrated in obese and normal rats (125). Few studies have been conducted on humans and further studies using large sample sizes are required to confirm these results. Experiments *in vitro* should clarify the molecular mechanisms involved in these activities.

Antiarthritic effects

Two previous studies found the antiarthritic activity of artichoke. Wauquier and colleagues (37) showed that ALE has a beneficial effect on osteoarthritis, performing an *ex vivo* exper-

iment using human articular chondrocytes. Another study demonstrated the beneficial effect of cynaropicrin on the metabolism of cartilage *in vitro* (126). These two scientific articles represent preliminary evidence that artichoke exerts antiarthritic activity and other studies are required to confirm these results.

Renoprotective activity

The renoprotective effect of artichoke intake has been demonstrated in studies involving animal models. Artichoke bud (42), leaf (25, 107), receptacle and stem (38) extracts may have a protective effect on renal function in rats. Khattab and colleagues (110) found that ALE exerts a beneficial effect on kidney function in a rat model of gentamicin nephrotoxicity.

Neuroprotective effects

ALE exerts a neuroprotective effect in rodent models and this effect may be mediated by the antioxidant activity of artichoke (61, 108). Future studies are needed to confirm these results.

Effects on the reproductive system

Previous studies found that ALE may ameliorate gonadal health in rat models through antioxidant effects (109, 112). The results show the potential beneficial effects of ALE on the reproductive system, but other studies are required to confirm these results and describe in detail the molecular mechanisms underlying these effects.

Effects on the immune system

The oral intake of artichoke may have positive effects on the immune system in animal models. A previous study by El-Boshy *et al.* (25) found that ALE is effective in improving the levels of immunostimulatory cytokines in a rat model of cadmium toxicity. Hueza and colleagues (127) showed that an artichoke extract exerts immunomodulatory activity in rats. These two studies provide the first evidence of the effects of artichoke on the immune system. Other studies are needed to confirm the results and explain the molecular mechanisms.

Antiphotoaging effects

Cynaropicrin has antiphotoaging effect *in vivo* and *in vitro* by regulating the nuclear factor kappa B (NF-kB) signaling pathway (128). Takei and colleagues (105) showed that this bioactive compound from artichoke may prevent ultraviolet B (UVB)-induced photoaging in human keratinocytes through antioxidant effects. These results should be confirmed by future studies.

Antifungal effects

Only one research study showed the antifungal activity of different artichoke extracts *in vitro* and found that ALE is the most effective. The authors analyzed the effect against *Candida albicans*, *Candida lusitaniae*, *Saccharomyces cerevisiae*, *Saccharomyces carlsbergensis*, *Aspergillus niger*, *Penicillium oxalicum*, *Mucor mucedo* and *Cladosporium cucumerinum* (129). Further studies should corroborate these results.

Prevention of periodontal diseases

Cynaropicrin from artichoke may exert a preventive effect on periodontal diseases *in vitro* by modulating the NF-kB signaling pathway (130). Only one study found this activity and these results should be confirmed.

This review has some limitations. We reported only scientific articles published in PubMed indexed journals, personal criteria were utilized for conducting the literature search and many studies are characterized by small sample sizes or require replication of results.

CONCLUSIONS

In this study, we show the health-promoting properties of artichoke after performing a literature search. The most common beneficial effects of this plant are those on the liver and lipid profile and antioxidant activity. Other health benefits include improved gastrointes-

tinal and cardiovascular health and anticancer, antimetabolic and antiobesity, prebiotic and probiotic, antidiabetic and renoprotective effects. Only a few studies found the beneficial effects of artichoke on the immune system, the reproductive system, the nervous system, arthritis, photoaging, periodontal diseases and fungal infections. Phenolics are the bioactive compounds mainly involved in these properties and ALE is the extract most utilized for these purposes. Many experiments have been conducted on animal models or *in vitro* and research studies involving humans would be helpful to clarify the beneficial effects of artichoke on human health. The health benefits of artichoke are well documented in scientific literature. Further studies should confirm the results of the articles reported in this review and the molecular mechanisms involved in the health-promoting properties of this plant.

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ETHICS

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Conflict of interests

The Authors declare that they have no conflict of interests.

Availability of data and material

Data and material are available on request from the Authors.

Authors' contributions

ADN, FG, FP and PZ conceptualized and designed the study. ADN conducted the literature search and drafted the article. All Co-authors discussed the findings, critically revised the article and approved the final version of the manuscript.

Ethical approval

N/A.

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REVIEW

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RETHINKING POST-MORTEM TRYPTASE: A CRITICAL ANALYSIS OF ITS ROLE IN DIAGNOSING ANAPHYLACTIC DEATHS

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SUMMARY

Post-mortem tryptase is used to support the diagnosis of anaphylaxis. However, despite its common use, the interpretation of elevated tryptase levels is still debated among experts. This review critically examines the use of post-mortem tryptase levels to identify fatalities resulting from anaphylaxis within forensic pathology. By synthesizing data from multiple studies, we aim to evaluate the reliability and consistency of post-mortem tryptase as a marker for anaphylactic deaths. Our methodical approach sheds light on the complexities and potential confounding factors in interpreting elevated tryptase levels. The findings suggest that the current understanding of post-mortem tryptase may require cautious interpretation and highlight the need for a more nuanced approach in forensic examinations. This review calls for a reassessment of existing methodologies and encourages further research to enhance our understanding in this crucial area of forensic science.

Key words
Tryptase; post-mortem levels; anaphylaxis; forensic pathology.

Impact statement
This study suggests that the current understanding of *post-mortem* tryptase may require cautious interpretation and encourages further research to better understand its role.

BACKGROUND

Tryptase: biological functions and significance

Tryptase is a trypsin-like protease, present mainly in the secretory granules of mast cells. Its release is typically related to mast cell activation, a phenomenon that can occur during allergic reactions, including anaphylaxis (1, 2). Tryptase is an essential enzyme of the human immune system, necessary for allergic reactions, inflammation and other immune defense processes (3, 4).

Anaphylaxis represents a serious and potentially life-threatening allergic response. It manifests itself with symptoms including difficulty breathing, decreased blood pressure and skin reactions. In the case of a living individual, the diagnosis of anaphylaxis is based primarily on clinical evaluation, supplemented by the presence of elevated serum tryptase concentrations. Serum mast cell tryptase (MCT) plays a critical role in facilitating

the diagnosis of anaphylaxis (5). However, when it comes to post-mortem analysis, the interpretation of tryptase levels presents substantial challenges, thus complicating the determination of death from anaphylaxis (6-8).
The prescribed clinical threshold for total tryptase appears insufficient in post-mortem scenarios, mainly due to largely unexplored factors leading to considerably elevated levels in such samples (5). As a result, there is currently a lack of a universally accepted threshold for diagnosing deaths caused by anaphylaxis.
In the context of post-mortem examinations, existing literature recommends rapid sampling of femoral blood for tryptase analysis immediately after death. Establishing a post-mortem tryptase threshold presents formidable challenges for several reasons (5, 9). The clinically approved 95th percentile value for tryptase, set at 11.4 mg/L, has limited relevance in the post-mortem setting, as various processes and conditions can exert an influence on tryptase levels (10, 11).
Instead, a proposed post-mortem threshold of approximately 43/44 µg/L serves as a benchmark for the biochemical diagnosis of anaphylaxis in several studies (9, 11). This differentiation has immense significance as numerous non-anaphylactic causes of death, and peri/post-mortem conditions have the potential to increase post-mortem tryptase levels making the adoption of tryptase for confident diagnosis questionable.

TRYPTASE IN POST-MORTEM ANALYSIS

Historical perspective and current practices

The historical progression of tryptase quantification in the field of forensic pathology has been a journey marked by noteworthy milestones and technological advancements. This evolution mirrors the increasing significance of biochemical markers in comprehending post-mortem occurrences and their implications in forensic inquiries (12).
The initial utilization of tryptase as a marker in forensic pathology can be traced back to the latter part of the 20th century. In its early stages, tryptase measurement relied on fundamental enzymatic assays. However, these assays were marred by limitations in terms of sensitivity and specificity, occasionally leading to ambiguous interpretations within the context of forensic pathology (12).
The emergence of more sophisticated techniques, such as enzyme-linked immunosorbent assay (ELISA), heralded a substantial enhancement in the quantification of tryptase. ELISA offered heightened sensitivity and specificity, facilitating more precise assessments of tryptase levels (13). Subsequently, advancements in mass spectrometry provided an even more precise methodology for quantifying tryptase, enabling the detection of minuscule quantities with remarkable accuracy (14, 15).
Contemporary forensic pathology places great emphasis on the timing of sample collection and the specific site of collection. Tryptase levels can exhibit significant variations based on these factors (16). Common sites for sample collection encompass cardiac blood, peripheral blood, and, on occasion, vitreous humor.
Presently, ELISA remains a widely adopted approach for tryptase measurement due to its equilibrium between accuracy, accessibility, and cost-effectiveness. Nevertheless, in intricate scenarios or when minute concentrations necessitate measurement, techniques such as liquid chromatography-mass spectrometry (LC-MS) are employed (14, 15).
Interpreting tryptase levels in a post-mortem context necessitates a nuanced comprehension of diverse factors, including decomposition, potential allergic reactions prior to death, and other underlying medical conditions (8). Modern forensic pathology integrates data from tryptase levels with other biochemical, histological, and circumstantial evidence to formulate comprehensive conclusions.
The utilization of tryptase measurement has evolved from being a novel biochemical marker to becoming a standard instrument in forensic pathology (17). Forensic pathologists, toxicologists, and medical researchers persist

in exploring the frontiers of tryptase measurement, including its role in distinguishing post-mortem intervals and its interactions with other post-mortem biochemical changes.

TRYPTASE: BIOCHEMISTRY AND PHYSIOLOGY

Molecular characteristics of tryptase

Tryptase possesses a distinctive characteristic among serine proteases due to its tetrameric structure, which plays a vital role in its enzymatic function (1, 17). This structure comprises four identical subunits, each contributing significantly to the enzyme's stability and specificity. In humans, the TPSAB1 gene encodes this enzyme, which can be categorized into two primary forms: alpha-tryptase and beta-tryptase.

Beta-tryptase, the form most relevant to anaphylaxis, is stored within the secretory granules of mast cells and is released upon the activation of these specialized mature blood cells, which have a distinct role in immediate hypersensitivity reactions (12, 18). However, mast cells also play a role in various other inflammatory-related processes, including conditions such as arthritis and multiple sclerosis.

Mast cells release two principal isoforms of tryptase: alpha-tryptase and beta-tryptase (6). Beta-tryptase is considered the predominant factor in anaphylaxis, whereas alpha-tryptase exerts distinct effects, particularly influencing the recruitment of inflammatory cells, including a reduction in neutrophil recruitment.

In the context of anaphylaxis, mast cell degranulation is initiated by the cross-linking of IgE molecules attached to the cell's IgE receptors by specific antigens (4, 6). This cross-linking leads to the release of stored tryptase. The precise mechanisms governing the role of tryptase in anaphylaxis remain elusive, although it demonstrates a notable preference for cleaving substrates at the C-terminal side of arginine and lysine amino acids, a characteristic it shares with the pancreatic enzyme trypsin, from which it derives its name (6).

The metabolic pathways of tryptase are not yet comprehensively understood; however, it is well-established that renal clearance is not the primary mode of elimination, with the liver being responsible for its catabolism (1, 6).

Functions of tryptase in the human body

The primary role of tryptase is to cleave and activate specific proteins and peptides, serving as a crucial participant in a variety of physiological processes. These processes encompass the immune response, because tryptase plays a pivotal role in immune defense mechanisms, particularly in allergic reactions and inflammation and its function involves the degradation of allergens, activation of complement proteins, and facilitation of immune cell recruitment to the inflammatory site (1, 17), and the regulation of cell function, because tryptase possesses the capability to influence the behavior of diverse cell types, including epithelial cells, fibroblasts, and smooth muscle cells and it exerts an impact on processes such as cell proliferation and apoptosis (4, 6).

Tryptase and allergic reactions

In the context of allergic reactions, especially in cases of anaphylaxis, tryptase assumes a central role. Following exposure to an allergen, mast cells undergo degranulation, liberating tryptase in conjunction with other mediators, notably histamine (6, 17, 19).

This liberation initiates the characteristic manifestations of an allergic response, including vasodilation, heightened vascular permeability, and contraction of smooth muscle. Consequently, heightened levels of tryptase serve as a distinguishing feature of mast cell activation during allergic reactions (1, 12).

Regulation of tryptase release

The release of tryptase from mast cells is meticulously regulated and occurs under specific circumstances:

1. **Allergen exposure**: the most prevalent trigger for tryptase release is exposure to

particular allergens, leading to IgE-mediated mast cell degranulation (17, 19).
2. **Physical and emotional stress**: physical trauma or emotional duress can also induce non-IgE-mediated mast cell activation and subsequent tryptase release (1, 4, 6, 12).
3. **Pharmacological agents**: specific medications and toxins can either directly or indirectly stimulate mast cell degranulation, resulting in elevated tryptase levels. Examples of such substances encompass opioids, muscle relaxants, and particular antibiotics such as vancomycin (20, 21). Radiocontrast media, employed in medical imaging procedures, can also prompt mast cell activation. Moreover, certain toxins, such as those found in venomous bites or stings, can evoke a similar response.

Mechanisms of tryptase release in allergic reactions

The release of tryptase during allergic reactions is primarily mediated via an IgE-dependent mechanism. This process encompasses several pivotal stages.
The first phase is the sensitization, the initial exposure to an allergen that initiates the production of specific IgE antibodies, which bind to high-affinity receptors (FcεRI) situated on the surface of mast cells (1, 4, 6, 8, 19).
The second phase includes subsequent exposure and cross-linking; upon subsequent exposure to the same allergen, the allergen molecules form cross-links with the IgE antibodies bound to the mast cells, thereby initiating a signaling cascade (4, 6).
Subsequentially occurs the mast cell degranulation where this signaling cascade culminates in the degranulation of mast cells, resulting in the release of tryptase, as well as other mediators such as histamine and leukotrienes (1, 4, 6, 8, 19-21).
All this leads to an augmentation of the allergic response where tryptase, in conjunction with other mediators, intensifies the allergic response by augmenting vascular permeability, attracting immune cells, and inducing smooth muscle contraction (4, 6).

Tryptase's role in anaphylaxis

Anaphylaxis is the most severe manifestation of an allergic response, characterized by a systemic release of mediators from mast cells and basophils. Tryptase plays a fundamental role in this process, contributing to the broad manifestations observed in anaphylaxis, including cardiovascular effects, since tryptase could induce vasodilation and increased vascular permeability, resulting in hypotension and shock, both crucial characteristics of anaphylaxis. (1, 6, 8, 17). Respiratory effects, given its role in bronchoconstriction and high mucus production, which leads to breathing difficulties (1, 4, 8, 17) and skin symptoms, since it is implicated in the development of the skin manifestations characteristic of anaphylaxis, such as urticaria and angioedema (1, 4, 8, 12, 18).
Histological analysis in cases of elevated tryptase levels, especially anaphylaxis, typically reveals mast cell degranulation, evidenced by dispersed granules within tissues and spleen (22, 23). Accompanying this are increased eosinophils and other inflammatory cells, indicating an allergic response. Additional histological signs may include edema and vascular congestion, supporting an allergic or anaphylactic etiology (24-30).

TRYPTASE IN CLINICAL DIAGNOSIS

In a clinical context, serum tryptase concentrations are assessed to facilitate the diagnosis of allergic responses, notably anaphylaxis.
The precise timing of sample acquisition is of paramount importance, as tryptase concentrations usually reach their zenith 1 to 2 hours following exposure to an allergenic substance and subsequently regress to their baseline levels within a 24-hour period (6, 8).
The measurement of serial MCT is considered the gold standard in aiding with the distinction between anaphylaxis and its clinical mimics (11). There has been a high degree of variation reported for the performance characteristics of MCT assays for anaphylaxis due to multiple factors, including variance in the definition

of anaphylaxis, diversity in the approach to MCT interpretation, heterogeneity in the clinical context of anaphylaxis, different causative agents, and the time of blood sampling (6, 8). Furthermore, other new biomarkers other than tryptase have been investigated for potential use in anaphylaxis. These include platelet activating factor, chymase, carboxypeptidase A3, dipeptidyl peptidase, basogranulin, and CCL-2. Apart from anaphylaxis, other clinical conditions could have increased tryptase levels (8).
Other conditions are chronic renal failure, hematological disorders such as myelodysplastic syndromes, acute and chronic myeloid leukemia, chronic eosinophilic leukemia, acute cardiac deaths, and others (6, 31). It has also been estimated that approximately 20% of the general population has an elevated baseline tryptase due to hereditary alpha-tryptasemia, which is an autosomal dominant condition that results from an increased number of germline copies of the alpha-tryptase gene (8).
Table I shows post-mortem tryptase levels for various clinical conditions. This factor contributes significantly to the inability of tryptase levels to serve as a reliable diagnostic indicator of post-mortem anaphylactic conditions. For example, in the case of acute cardiovascular deaths (ACD), tryptase levels can vary significantly depending on whether they occur with or without acute coronary syndrome (ACS), as indicated in the study by Xiao *et al.* (31). These examples show us how there are confounding factors in the diagnosis of death from anaphylaxis and how tryptase, despite being a credible diagnostic criterion today, must be associated with other factors before considering death for allergic reasons.

Challenges in interpretation

What is crucial for the understanding of post-mortem analysis is that raised levels of tryptase may be caused by a wide range of non-anaphylactic factors (8).
The increase in the concentrations of tryptase as a result of prolonged agonal states may be quite significant (2). During these periods, the human body experiences substantial stress and a lack of oxygen, leading to a cascade of biochemical reactions, including the activation of mast cells. This is most evidently occurring in cases of cardiac arrest or respiratory failure, where a resultant extended lapse of oxygen plays a critical role.

Table I. The table outlines various clinical conditions alongside corresponding tryptase levels, the timing of findings, and their sensitivity and specificity, where applicable.

Clinical Condition	Tryptase Levels	Timing of finding *	Sensitivity	Specificity	References
Anaphylaxis	12.3-309.0 ng/mL	Post-mortem	90%	92.1%	Xiao *et al.*, Tse *et al.*
Acute cardiovascular death (ACD)	3.2-18.9 (non-ACS); 8.0-188 (with ACS)	Post-mortem	NA	NA	Xiao *et al.*
Acute aortic dissection	9.0-36.0 ng/mL	Post-mortem	NA	NA	Xiao *et al.*
Pneumonia	3.8-8.0 ng/mL	Post-mortem	NA	NA	Xiao *et al.*
Asphyxia	10.9 (1.6-57.2) Femoral	Post-mortem	NA	NA	McLean-Tooke *et al.*
Trauma	13.7 (2.7-131.2) Femoral	Post-mortem	NA	NA	McLean-Tooke *et al.*
Sepsis	9.6 (2.1-18.0) Femoral	Post-mortem	NA	NA	McLean-Tooke *et al.*
Intracranial hemorrhage (ICH)	14.9 (9.8-107.0) Femoral	Post-mortem	NA	NA	McLean-Tooke *et al.*

* The timeframe for tryptase measurement after death is not detailed beyond the general post-mortem status in the articles analyzed.

The reason for the increase in tryptase levels in the context of sepsis is the systemic inflammatory response of the body (6). Sepsis often evolves into a condition called systemic inflammatory response syndrome (SIRS); in this case the activation of the immune system is not localized but extensive, resulting in the release of various mediators, including tryptase. The increase in this indicator signals the body's response to a serious infection: it is not limited only to anaphylactic reactions.
As for the surge in tryptase levels prompted by trauma itself, the reason is the correlation between this factor with the actual physical damage to tissues and cells (1). There is no doubt that trauma, especially of a severe or blunt nature, causes immediate mast cell degranulation, which causes the synthesis of tryptase and its release into the bloodstream. The reaction is undoubtedly part of the body's immediate response to the injury and is aimed at speeding up the recovery process.

Challenges in interpreting tryptase levels in anaphylaxis

While elevated tryptase levels can serve as an indicative marker of mast cell activation, their interpretation within the context of anaphylaxis, especially in post-mortem scenarios, poses considerable challenges owing to the following factors:

1. **Variability in peak levels**: the presence of individual variability in the highest recorded tryptase levels further complicates the final formulation of a specific diagnostic threshold (5, 6, 9). This result can also be found in the study by Tse *et al*. (5), who identified an optimal cut-off of 53.8 ng/mL for post-mortem total tryptase in femoral blood to diagnose anaphylaxis, with a sensitivity of 89% and specificity of 93% (9).
2. **Influence of basal tryptase**: individuals with elevated levels of basal tryptase, often associated with conditions such as mastocytosis, may exhibit distinct peak tryptase levels during anaphylactic episodes (17, 32). Conditions that increase basal tryptase, such as acute myelocytic leukemia, various myelodysplastic syndromes, and end-stage renal disease, may affect the interpretation of peak levels.
3. **Timing of sample collection**: It is clear that the transient increase in tryptase compromises the independent assessment of tryptase levels unless it is collected within the specified period post-anaphylaxis (5, 6, 8, 12, 16). The study by Garland notes that tryptase begins to increase within 15-30 minutes of anaphylaxis, peaks in 2 hours, and then decreases to the normal range within 24 hours. Furthermore, the study reiterates that the time from when ante-mortem tryptase samples were obtained or the duration of survival post tryptase peak could affect results. If only post-mortem samples are available, then negative results may be biased (6).

Biochemical properties of tryptase and relevance in post-mortem analysis

Tryptase exists in various isoforms, with beta-tryptase being particularly pertinent in the context of anaphylaxis. The enzyme's resilience after death plays a pivotal role in its applicability for forensic investigations. Unlike numerous other proteins, tryptase retains a degree of durability following demise, enabling its analysis post-mortem. However, this durability is subject to variations influenced by factors such as the post-mortem interval, environmental conditions, and the manner of demise (6, 17).
For example, Xiao *et al*. found that tryptase levels were elevated in groups described as anaphylactic deaths, acute cardiovascular deaths, and acute dissecting aneurysm ruptures compared to control groups, and suggested a cutoff of 43 ng/mL owing to the high degree of sensitivity and specificity in discriminating anaphylactic deaths (31).
Garland *et al*. found that the reference range for post-mortem tryptase in groups that are non-anaphylactic deaths is <23 µg/L, and they further understood that age, post-mortem interval, resuscitation, and the cause of death did not significantly influence the tryptase levels presented that the design technique is used (6).

The fact that different studies use different cutoff levels for making their recommendations makes it clear why it is essential to continue researching and debating the topic. The range from a cutoff of 43 ng/mL to a high of over 100 ng/mL shows that the current cutoff levels are flawed and, when coupled with abnormal values, show how necessary it is to evaluate all the evidence when making this determination (5, 7, 9, 16).

The National Institute for Health and Clinical Excellence (NICE) has identified post-mortem serum tryptase testing as a very important tool in those situations where anaphylaxis emerges as a potential cause of death. Although NICE does not establish a specific cutoff value, it points out the necessity of considering elevated tryptase levels along with the clinical history and autopsy data to sustain the final diagnosis of anaphylactic reaction (33).

The Royal College of Pathologists (RCPath) in the United Kingdom also refers to post-mortem tryptase analysis in its guidelines on autopsy practice and claims that it should be requested in cases of sudden, unexplained death and anaphylaxis is a probable cause. RCPath also acknowledges the fact that elevated tryptase levels do confirm an anaphylactic reaction yet should be solely one warrant of the correct conclusions and be analyzed with the general understanding of the case, including possible confounders as a post-mortem interval (PMI) or an intensive resuscitation (34).

The European Academy of Allergy and Clinical Immunology (EAACI) has published a comprehensive guideline on the diagnosis and management of anaphylaxis which, although primarily focused on clinical settings, indirectly support the forensic application of the presented method because they emphasize the biological rationale of tryptase, its mechanism, and patterns of release during the anaphylactic reaction. Moreover, the Academy also highlights that this agent is a highly specific marker of mast-cell degranulation, which aids it in the identification of an anaphylactic phenomenon if used correctly (35).

Challenges in measuring post-mortem tryptase levels

One of the foremost challenges encountered when interpreting post-mortem tryptase levels lies in the inherent variability of measurement methodologies. Diverse assays and techniques may produce disparate outcomes, and the absence of a standardized post-mortem tryptase level adds an additional layer of complexity to the interpretation process (6, 12).

Furthermore, the post-mortem interval, which denotes the time elapsed between the individual's demise and the collection of samples, exerts a profound influence on tryptase levels. The processes of degradation initiated after death can induce alterations in tryptase concentrations, potentially leading to erroneous conclusions (8, 17). Additionally, the physiological condition of the deceased at the time of demise, such as factors like stress or hypoxia, can also exert an impact on mast cell activation, thereby affecting the release of tryptase (1) (**Table II**).

Table II. Various considerations affecting the measurement and interpretation of tryptase levels in both post-mortem and clinical contexts.

Issue	Post-mortem	Clinical	References
Reference values	Variability across studies and lack of universally accepted cut-off values complicate establishing a universal level for post-mortem diagnosis of anaphylaxis	The reference values established clinically cannot be used to determine if the tryptase levels are consistent with sampling time and hence may not be easily used for post-mortem analysis	Xiao *et al.*, 2017; Tse *et al.*, 2018

Influence of post-mortem interval (PMI)	The elapsed time after death before sample collection can significantly affect tryptase levels, adding a layer of complexity to their interpretation	The PMI, which refers to the time elapsed after death before sample collection, does not have a clinical context as tryptase is collected while living	Xiao *et al.*, 2017; Tse *et al.*, 2018; NICE clinical guideline
Effect of resuscitation efforts	Resuscitation efforts, such as cardiopulmonary resuscitation (CPR), may artificially elevate tryptase levels due to induced trauma to mast cells	Tryptase levels may be influenced by resuscitation efforts, such as CPR, due to trauma inflicted onto mast cells, thereby increasing the release; however, this does not have any clinical value as the main area of focus is immediate medical history	Xiao *et al.*, 2017; NICE clinical guideline
Sampling site and technique	The choice of sampling site and method can influence tryptase levels, with a preference for femoral blood to reduce variations	The technique and data collection site in clinical contexts are peripherally sited compared to the preference in post-mortem collection, which is femoral to minimize differences.	Tse *et al.*, 2018
Confounding conditions	Pre-existing conditions such as cardiovascular diseases, trauma, and substance use can complicate the interpretation of tryptase levels in a post-mortem context	Confounding or preexisting conditions in the clinical context, such as systemic or chronic cases also have an effect on tryptase, while post-mortem conditions show the likelihood of concomitant diseases such as cardiovascular disease (CVD)	Tse *et al.*, 2018; EAACI anaphylaxis guideline
Variability in levels	There is considerable variability in measured post-mortem tryptase levels, necessitating standardization in measurement methodologies	Tryptase levels in a clinical setting follow a more predictable pattern post-anaphylactic event	Tse *et al.*, 2018
Interpretation in the context of sudden death	Tryptase analysis can be particularly useful in cases of sudden death where the cause is not immediately apparent	Analysis in case of sudden death is mainly to ascertain that the cause is due to the anaphylaxis condition, but in clinical contexts, it helps confirm the suspicion	Xiao *et al.*, 2017; Tse *et al.*, 2018
Influence of post-mortem factors	Factors such as decomposition and environmental variations can affect tryptase levels, adding further interpretative challenges	Factors influencing PM the decomposition phase and environmental factors are not applicable in clinical cases	Xiao *et al.*, 2017

THE ROLE OF TRYPTASE IN FORENSIC PATHOLOGY

In the field of forensic pathology, the examination of tryptase levels is utilized to offer insights into potential factors contributing to the cause of death. Historically, heightened levels of tryptase in post-mortem specimens have conventionally been regarded as indicative of anaphylactic reactions (6, 12). Nevertheless, owing to the intricate and variable nature of post-mortem alterations, a careful approach must be adopted when interpreting this data (8, 17).

It is imperative to possess a comprehensive understanding of the intricate biochemistry of tryptase and the various factors that can impact its levels post-mortem in order to arrive at precise conclusions regarding the cause of death (1).

Relationship between anaphylaxis and post-mortem tryptase levels

Anaphylaxis, owing to its inherent characteristics, instigates a swift discharge of tryptase from mast cells. In individuals who are still alive, a noteworthy surge in serum tryptase concentrations subsequent to exposure to an allergen serves as a pivotal diagnostic indicator for anaphylaxis (3, 32).

Nevertheless, in the post-mortem scenario, this association assumes a more intricate nature. Elevated tryptase concentrations are indeed frequently detected in instances where anaphylaxis is established as the underlying cause of demise. However, it is imperative to grasp that these heightened levels are not solely confined to fatalities resulting from anaphylaxis (10).

In instances of fatalities attributed to anaphylaxis, post-mortem tryptase concentrations generally exhibit an elevated profile when compared to individuals who succumbed to alternate causes (3, 11, 12). Nevertheless, it is essential to note that the range of these concentrations can be considerably wide, and the establishment of a universally accepted 'threshold' value that unequivocally signifies anaphylaxis remains elusive (6, 36).

The research contributions by Xiao *et al*. (31), and Tse *et al*. (9) present valuable findings on the forensic applicability of post-mortem tryptase measurements.

Firstly, on the marked elevation of tryptase in anaphylactic deaths compared to other causes of high levels of the enzyme, Xiao *et al*. proposed a cut-off value of 43 ng/mL for distinguishing anaphylactic from acute cardiovascular deaths (31).

Secondly, Tse identified the optimal cut-off value to be 53.8 mg/L for diagnosing anaphylaxis in post-mortem while reporting sensitivity and specificity of 90% (9).

However, the widespread of factors such as the post-mortem interval, hemolysis, trauma, and swabbing affected by various substituent such as body conditions compounds the attainment of a single threshold value that holds across all cases (6, 7, 9). For example, the post-mortem interval and conditions of storage can affect the degradation or preservation of tryptases, and hence the ability to measure its levels.

Tryptase levels in non-anaphylactic deaths

Certainly, it is of utmost importance to note that elevated tryptase levels have also been detected in cases unrelated to anaphylaxis. Factors such as asphyxiation, cardiac arrest, and even traumatic injuries can result in elevated tryptase levels (3, 10, 37, 38). The underlying causes for this phenomenon are multifaceted, encompassing stress-induced mast cell degranulation, destabilization of mast cells due to hypoxic conditions, and post-mortem autolytic processes (2, 21, 37).

These discoveries underscore the necessity for prudence when ascribing heightened post-mortem tryptase levels exclusively to anaphylactic reactions (4, 6).

The literature stresses that several factors than anaphylaxis may elevate post-mortem tryptase levels. For example, the level of post-mortem tryptase following drug overdose, especially heroin or other opioids, may be raised. One of the reasons it could do so is the capability of

these substances to catalyze non-specific mast cell degranulation, which can discharge mast cell granule items including tryptase. Thus, the increase in the level of tryptase may signal about the prevalence of an anaphylactoid mechanism of death (6, 7).
Secondly, sudden infant death syndrome (SIDS) has been observed to be another cause of post-mortem tryptase levels. Nonetheless, not all circumstances of SIDS appear to have an association, and even when the IgE-mediated allergic or anaphylactic reaction is accompanied by an elevated tryptase level, it may be inferred that agonal asphyxia, or some other process was among factors also increasing the tryptase level. It remains unclear what causes SIDS to produce post-mortem elevation of tryptase, thus, it may signal the complexity of reading post-mortem tryptase responses (6).
In patients with trauma, the post-mortem level of tryptase is often increased. The trauma site does not have to be centralized to have a significant influence on the tryptase level. Thus, either direct mast cell injury or lysis causing the release of tryptase, or the huge physical stimulus induced by trauma that produced a release from pulmonary and gastrointestinal mast cells are suggested to be the likely mechanisms. Therefore, trauma, even if the sampling is peripheral, is a substantiated cause of increased post-mortem tryptase level (6, 7, 31).
Furthermore, post-mortem tryptase levels during cardiovascular death increase, especially in acute coronary syndrome and acute dissecting aneurysm. Accordingly, the median tryptase level is highest in acute dissecting aneurysm, then followed acute coronary syndrome and total acute cardiac death, with wide intervals within each group, which offers a small if any practicable use. (6).

Implications for forensic interpretation

In conclusion, the available evidence suggests that, despite the high post-mortem tryptase levels having some meaning as a strategically useful marker (11), it is crucial not to base the diagnosis of anaphylactic deaths solely on this parameter (6).
To ensure as comprehensive and accurate forensic assessment as possible, additional contributing factors, such as the victim's existing medical conditions and previous history, immediate circumstances of their death, and various post-mortem examination results, must be considered as well (6, 39).

Implications for post-mortem analysis

The timing of death in relation to the onset of anaphylaxis, the time interval between death and sample collection, and the phenomenon of postmortem tryptase redistribution markedly influence postmortem tryptase (P-MTP) levels and should be taken into consideration when evaluating P-MTP levels for post-mortem diagnosis of anaphylaxis. Tryptase, although always present at a certain background level, reaches its peak between 30 minutes and 2 hours. After release, tryptase levels are deactivated or removed and return to normal within 12 to 72 hours (5, 9).
This dynamic of early release, deactivation, and removal of tryptase generates early release, but longer-lived tryptase levels highlight the importance of time-of-death (DTOD) offset determination. PMI influences current sampling. The slight increase in P-MTP with PMI has been recorded in previous research, with one review finding an increase from 6 mg/L at death to 8.8 mg/L after two days post-mortem (6, 16). However, this increase is not strong enough to exceed the proposed threshold for post-mortem diagnosis of anaphylaxis and demonstrates that PMI has minor effects on P-MTP but can be minimized by early sampling.
The phenomenon of post-mortem preservation of various molecules in immune cells could hypothetically be intensified by collection from or near mast cell-rich organs such as the heart or lungs (6, 7).
All these factors demonstrate the need for careful consideration of P-MTP levels in forensic practice. Release and elimination kinetics,

the impact of PMI and PPP (post-mortem retention phenomenon) all require special attention to adequately evaluate the role of anaphylaxis in sudden death.

Therefore, although tryptase is a useful indicator for identifying anaphylactic reactions, its use in determining the cause of death must be carefully considered. This involves examining these issues in the broader field of forensic pathology.

The influence of sampling sites and method on post-mortem tryptase measurement significantly impacts the accuracy of forensic pathology assessments. Variations in sampling techniques and locations can affect tryptase levels, complicating the diagnosis of anaphylactic deaths.

Tryptase levels may increase slightly post-mortem, but timely sampling mitigates this effect. Femoral blood is preferred due to its lower susceptibility to contamination and post-mortem changes compared to cardiac blood (40, 41). Standardization of sampling procedures is essential to minimize variations caused by different techniques and ensure reliable results.

The femoral vein clamp and aspiration technique involves occluding the femoral vein immediately after death to prevent blood redistribution. The blood is then drawn up using a sterile syringe. This method preserves the integrity of ante-mortem tryptase levels (16, 42). Consistent sampling allows for the development of robust cut-off levels for postmortem tryptase, addressing variability issues noted in previous studies (*e.g.*, 43 ng/mL by Xiao *et al.*, and 53.8 ng/mL by Tse *et al.*). By standardizing the collection process, the technique reduces false positives and negatives, improving overall diagnostic accuracy.

DISCUSSION

Initial research has established tryptase as a key marker for anaphylaxis in post-mortem examinations, laying the foundation for its widespread acceptance in forensic pathology. This marker, introduced through pioneering work in the late 1990s, was initially celebrated for its potential to differentiate between anaphylactic deaths and other causes. However, as the field progressed, further studies began to uncover certain limitations in the use of post-mortem tryptase levels.

These investigations have highlighted the need for a nuanced interpretation of tryptase levels. It has become evident that while tryptase is a valuable indicator, its levels can be affected by various factors, including acute cardiovascular events and changes that occur after death. This understanding calls for a critical reassessment of the diagnostic reliability of tryptase in forensic pathology, especially in suspected cases of anaphylaxis.

An essential aspect of interpreting post-mortem tryptase levels accurately involves understanding the methodologies used for its measurement. The significance of the post-mortem interval and the method of sample collection has been emphasized. Variations in sampling techniques can significantly impact the measured levels of tryptase, suggesting that the selection of a collection method can greatly influence the results. Additionally, establishing reference values for MCT in post-mortem serum has helped address potential confounding factors in the measurement process.

The challenge of distinguishing deaths caused by anaphylaxis from those resulting from other causes, based solely on tryptase levels, has become increasingly apparent. Research has shown that elevated tryptase levels can be present in both anaphylactic and non-anaphylactic deaths, indicating that high levels of tryptase are not solely indicative of anaphylaxis. This revelation underscores the importance of careful interpretation, particularly in the analysis of suspected anaphylactic deaths.

Comparing tryptase with other biomarkers used in post-mortem examinations is crucial for understanding its relative effectiveness. This comparison is instrumental for forensic pathologists, enabling them to make informed decisions about the most reliable biomarkers for determining causes of death.

Investigating alternative biomarkers to tryptase in post-mortem analysis is essential for understanding their effectiveness in diagnosing anaphylactic deaths. Biomarkers such as IgE, histamine, and their derivatives have been examined for their potential in identifying anaphylactic reactions. Unfortunately, plasma histamine measurement is not feasible due to the short plasma half-life and the difficulties in handling the sample. In this regard, tryptase generally demonstrated better diagnostic performance than histamine. Research has highlighted the role of IgE as a potential supplementary indicator alongside tryptase, and serum total IgE has been used to confirm anaphylaxis when tryptase is elevated.
The effectiveness of tryptase compared to other biomarkers has been a continuous area of research. Studies have methodically evaluated the diagnostic use of serum tryptase in anaphylactic deaths, providing a comparative perspective with other markers used in forensic pathology. These comparative studies are crucial in assessing the reliability and accuracy of various biomarkers in distinguishing anaphylactic deaths from other causes.

CONCLUSIONS

A key future direction in this field is identifying and addressing research gaps. This includes exploring factors that affect post-mortem tryptase levels and the possibility of false positive results. There is a recognized need for further research on the stability and variability of post-mortem tryptase levels.
Future research could focus on large-scale studies comparing multiple biomarkers, including tryptase, in different post-mortem scenarios. Additionally, experimental designs aiming to understand the kinetics of tryptase release during various post-mortem intervals would be valuable. This could provide a clearer understanding of the biomarker's behavior and improve its diagnostic accuracy.
While tryptase remains a valuable biomarker, its interpretation in post-mortem cases is fraught with challenges due to various confounding factors and the lack of a standardized threshold level.
Despite the limited supporting data, forensic pathologists and investigators are encouraged to consider tryptase as part of a broader investigative framework, including additional clinical, pathological, and circumstantial evidence.
The future of post-mortem analysis of anaphylactic deaths depends on the development of more sophisticated and multidimensional diagnostic strategies. This includes further research into the mechanisms affecting tryptase levels and the exploration of additional biomarkers that can provide a more detailed and accurate insight into anaphylactic fatalities.

ETHICS

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Availability of data and material

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Authors' contributions

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Ethical approval

N/A.

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REVIEW

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A REVIEW OF METABOLIC SYNDROME: DIET, PHYSICAL ACTIVITY AND NATURAL REMEDIES

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SUMMARY

Metabolic syndrome (MetS) is a growing public health problem and is defined by the presence of at least three of five diagnostic criteria, which include impaired glucose metabolism, abdominal obesity, hypertension, high levels of triglycerides and low high-density lipoprotein cholesterol (HDL-C) levels. MetS increases the risk of type 2 diabetes (T2D), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), cancer and polycystic ovary syndrome (PCOS). In this narrative review, we describe the effects of diet, physical activity and natural remedies on the prevention and treatment of MetS, performing a literature search using PubMed and Google Scholar. The results of this work show that the Mediterranean diet, the energy-restricted Mediterranean diet and the healthy diet are promising dietary strategies for treating and preventing MetS. Other diets include the fat-modified diet, the carbohydrate-modified diet, the high-protein diet, intermittent fasting and the plant-based diet. Physical activity has beneficial effects on MetS, alone or in combination with a proper diet and natural remedies. Finally, natural remedies, such as unsaturated fatty acids, resveratrol, artichoke, berberine, probiotics and prebiotics, garlic, curcumin, pomegranate and olive polyphenols, may be helpful for the prevention and treatment of this condition. The results of many scientific studies described in this work should be confirmed. This narrative review shows that diet, physical activity and natural remedies are effective in preventing and treating MetS.

Key words
Metabolic syndrome; treatment; diet; physical activity; natural remedies.

Impact statement
Diet, physical activity and natural remedies are promising strategies for preventing and treating metabolic syndrome (MetS).

INTRODUCTION

Metabolic syndrome (MetS) encompasses different metabolic conditions and represents a growing public health problem worldwide. Many definitions of MetS are found in the scientific literature and the most commonly used are those of the World Health Organization (WHO) (1), the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (2) and the International Diabetes Federation (IDF) (3). MetS diagnosis requires the presence of at least three of five diagnostic criteria, which include abdominal obesity, impaired glucose metabolism, high levels of triglycerides, hypertension and low high-density lipoprotein cholesterol (HDL-C) levels. Hyperglycemia or insulin resistance and abdominal obesity are essential criteria in the WHO and

IDF definitions, respectively. The NCEP ATP III and IDF definitions share the same cut-off values, except for abdominal obesity.

The prevalence of MetS varies by age, sex and ethnicity. This condition becomes more common with age and the prevalence of each MetS factor and their combinations differs between males and females. For example, obesity is more common in females than in males (4, 5). Individuals with MetS are at increased risk of different medical conditions, including cardiovascular disease (CVD), type 2 diabetes (T2D), cancer, non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS). MetS is often due to inappropriate lifestyles, which include lack of physical activity and unhealthy diets, and a genetic predisposition (6, 7). Epigenetic modifications are of primary importance, as they can explain how genetics and environmental factors contribute to MetS (8).

In this narrative review, we describe the strategies for the prevention and treatment of MetS. We used the electronic databases, such as PubMed and Google Scholar, to find the scientific articles which show the role of nutrition, physical activity and natural remedies in MetS (**Figure 1**).

METABOLIC SYNDROME AND DIET

Healthy eating habits are relevant for the prevention and treatment of MetS and several studies have reported the beneficial effects of different types of diet on this condition.

Mediterranean diet and energy-restricted Mediterranean diet

The Mediterranean diet has been previously studied to find its role in MetS prevention and treatment. A research article by Babio *et al.* (9) showed that a Mediterranean diet which includes nuts or extra virgin olive oil can reverse MetS in a cohort of 3,392 individuals with this condition. They found a reversal of MetS in 958 individuals and a beneficial effect on hyperglycemia and central obesity. Another study showed the positive effect of this type of diet on MetS status in a sample of 424 individuals at risk of CVD (10). Riutord Sbert and colleagues (11) reported a decreased prevalence of MetS in 1,457 adults who followed the Mediterranean diet. Another study found that this type of diet is associated with a lower severity of MetS in a cohort of 5,739 overweight or obese individuals with MetS (12). Campanella and colleagues (13) showed that the Mediterranean diet, especially the Medi-

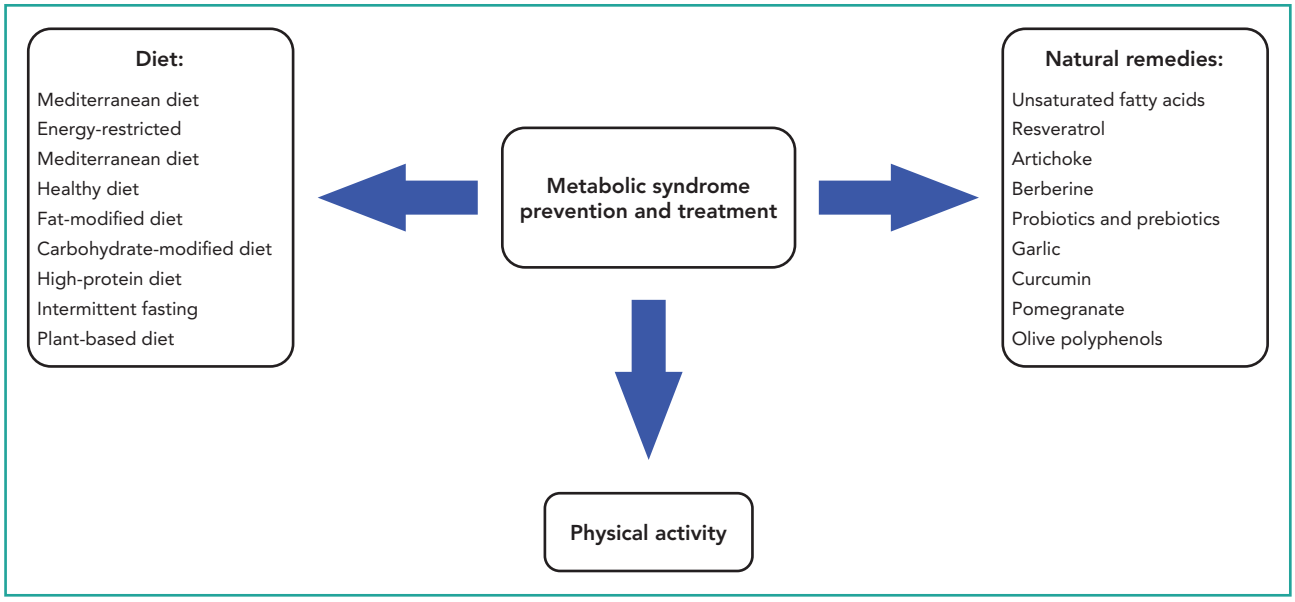

Figure 1. Metabolic syndrome. An illustration of the role of diet, natural remedies and physical activity in the prevention and treatment of this condition.

terranean low-glycemic index diet, is associated with lower levels of fasting remnant cholesterol, which is a predictor of CVD, in a sample of 237 individuals with MetS.

Most previous studies examined the effects of the energy-restricted Mediterranean diet on MetS. Two research articles found the beneficial effect of this type of diet in combination with physical activity on NAFLD and MetS in participants with these two conditions (14, 15). Álvarez-Álvarez and colleagues (16) showed a decreased risk of CVD in individuals following an energy-restricted Mediterranean diet, studying a sample of 6,874 overweight or obese participants with MetS. Other two studies found that this diet in combination with physical activity modifies the gut microbiota and has a beneficial effect on NAFLD (17) or cardiovascular health (18) in overweight or obese participants with MetS. Previous research articles showed the positive effect of an energy-restricted Mediterranean diet in combination with physical activity on body composition (19) and lipid profiles (20, 21) of overweight or obese individuals with MetS. Salas-Salvadó and colleagues (22) reported that an energy-restricted diet in combination with physical activity may exert beneficial effects on cardiovascular health and weight management in a cohort of 626 overweight or obese individuals with MetS.

Healthy diet

A diet characterized by healthy food intake is a promising choice for MetS prevention and treatment. Lankinen and colleagues (23) found the positive effect of a diet which includes fatty fish, bilberries and wholegrain products on HDL-C in individuals with MetS and impaired glucose metabolism. A study by Bub *et al.* (24) demonstrated that the intake of bioactive food is associated with increased HDL-C levels and decreased triglyceride levels in a sample of 167 individuals at risk of MetS. Another research article found the beneficial effect of food containing betaine or choline on cardiometabolic health, studying a cohort of 5,613 obese or overweight participants with MetS (25). Tremblay and colleagues (26) showed that high consumption of fibers improves metabolic health in 87 individuals with MetS. A previous study by Julibert *et al.* (27) found that the consumption of nuts may improve MetS, studying a sample of 5,800 obese or overweight participants with MetS. The moderate intake of red wine, which is high in polyphenols, has been found to decrease the prevalence of MetS in 5,801 individuals at risk of CVD (28). A study by Xiao *et al.* (29) showed that the intake of rice wine is associated with a decreased prevalence of MetS in a cohort of 37,582 individuals living in rural China. The high intake of ultra-processed food has been negatively associated with cardiometabolic health in a sample of 5,373 obese or overweight participants with MetS, providing evidence of the positive role of a healthy diet in MetS management (30). Low-fat milk and dairy products and yogurt have been found to have a beneficial effect on MetS prevention, studying a cohort of 1,868 individuals at risk of CVD (31). A previous study by Mohammadi-Sartang and colleagues (32) showed the positive effect of fortified yogurt intake on MetS factors in a sample of 87 overweight or obese individuals with MetS following an energy-restricted diet. Chen and colleagues (33) found that yogurt may have beneficial effects on insulin resistance and biomarkers of NAFLD in a cohort of 92 obese females with MetS and NAFLD.

Fat-modified diet

The beneficial effects of the fat-modified diet on MetS have been reported in previous studies. Egert and colleagues (34) found that an energy-restricted diet enriched with α-linolenic acid (ALA) ameliorates vascular and inflammatory biomarkers in a sample of 81 overweight or obese individuals with MetS. Another study showed the positive effect of a diet high in monounsaturated fatty acids (MUFAs) and a diet high in complex carbohydrates and low in fats with ω-3 long chain polyunsaturated fatty acids (PUFAs) supplements on insulin

resistance in individuals with MetS and insulin resistance (35). Two previous research articles showed the beneficial effect of diets rich in MUFAs on MetS and central obesity (36) or lipid-lipoprotein profile (37) in obese individuals with MetS or at risk of this condition. Diets rich in MUFAs or PUFAs have been reported to improve cholesterol function in obese participants at risk of MetS or with this condition (38).

Carbohydrate-modified diet and high-protein diet

A diet which includes healthy carbohydrates may exert a positive effect on MetS and CVD. Zamanillo-Campos and colleagues (39) found that this dietary strategy may reduce adiposity, studying a sample of 1,476 overweight or obese individuals with MetS. High consumption of wholegrain products and fibers has been described as the main factor. A study by Martínez-González *et al.* (40) demonstrated that high intake of healthy carbohydrates may reduce the risk of CVD in a sample of 5,373 overweight or obese participants with MetS.

The high-protein, low-glycemic index diet has been previously examined to find a possible beneficial effect on MetS. Two research articles showed that this dietary intervention may help to reduce weight, inflammatory biomarkers and insulin levels (41) or weight and leptin levels (42) in obese or overweight individuals with MetS.

A case report study by Bolos *et al.* (43) found that the ketogenic diet, which is characterized by low-carbohydrate and high-fat intake, may exert a positive effect on MetS and weight reduction in an obese adult male with MetS, following this diet combined with intermittent fasting. The results of this study should be confirmed.

Intermittent fasting

Intermittent fasting is a promising dietary strategy for preventing and treating different health conditions. This strategy has been studied to find possible beneficial effects on MetS. A previous research article showed that intermittent fasting has positive effects on weight reduction, HDL-C, triglycerides, systolic blood pressure and waist circumference in a sample of 100 individuals with MetS following an energy-restricted diet (44). Parvaresh and colleagues (45) found the beneficial effect of an alternate-day modified fasting diet, compared with an energy-restricted diet, on fasting plasma glucose, waist circumference, weight reduction and systolic blood pressure in a cohort of 69 overweight participants with MetS. A research article by Razavi *et al.* (46) demonstrated that this type of diet may exert a positive effect on weight management and coagulation and inflammatory biomarkers in a sample of 75 participants with MetS. Another study reported that a hepatic intermittent fasting diet plan is helpful in treating prediabetes and insulin resistance in 21 participants with MetS and insulin resistance or prediabetes (47). He and colleagues (48) showed that a time-restricted diet either alone or in combination with a low-carbohydrate diet may ameliorate MetS in individuals with this condition.

Plant-based diet

The health benefits of the plant-based diet have been reported in previous studies. Many studies have been focused on the benefits of the healthy plant-based diet. Oncina-Cánovas and colleagues (49) found that a pro-vegetarian diet, characterized by high intake of plant-derived food, and a pro-vegetarian diet which includes healthy food reduce the risk of CVD in a cohort of 6,439 overweight or obese individuals with MetS. Another study showed the beneficial effect of the healthful plant-based diet on MetS and waist circumference in a sample of 9,544 adult participants (50). A research article by Kim *et al.* (51) found a higher prevalence of MetS in individuals following an unhealthy plant-based diet, studying a cohort of 5,646 participants. Vajdi and colleagues (52) showed that an unhealthful plant-based diet may raise the risk of hyperglycemia in a sample of 347 obese participants. Another research article found that a healthy plant-based diet may lower the risk of central obesity and

MetS, studying a cohort of 10,013 adult participants (53).

METABOLIC SYNDROME AND PHYSICAL ACTIVITY

Physical activity has been reported to be a strategy for treating and preventing MetS. Previous studies showed that physical activity may be effective in reducing the prevalence of MetS in different study populations (11, 29, 54, 55, 56, 57, 58, 59, 60, 61, 62). Regular and high-intensity physical activity has been reported to reduce the prevalence of MetS, studying samples of 1,653 (63) and 27,788 (64) individuals. A research article by Pitsavos *et al.* (65) found that physical activity may have beneficial effects on coagulation and inflammatory biomarkers in a sample of 3,042 participants with or without MetS, highlighting the possible protective effect of this strategy on MetS by modulating coagulation and inflammation.
Previous studies demonstrated that physical activity may reduce the accumulation of visceral adipose tissue (66) and ameliorate body composition (67) in overweight or obese individuals with MetS. Another study found the beneficial effect of multi-component and power training programs using elastic bands on MetS in a sample of 72 overweight or obese elderly females with this condition (68). Two research articles showed the benefits of aerobic exercises in combination with resistance exercises on MetS in individuals with this condition (69) or with T2D and MetS (70). Physical activity may improve cardiovascular health in participants with MetS (71, 72). Another study found that moderate and high-intensity physical activity exerts a beneficial effect on CVD risk in a cohort of 5,776 overweight or obese individuals with MetS (73). Reljic and colleagues (74) showed the positive effect of low-volume high-intensity interval training on cardiometabolic and inflammatory biomarkers in a sample of 104 obese individuals with MetS. The severity of MetS has been reported to be decreased in participants with this condition (75) and in overweight or obese individuals with MetS (12) practicing physical activity. A study by Lau *et al.* (76) found the protective effect of Hatha yoga against MetS in participants with and without this condition. Another research article showed the anti-inflammatory activity of Hatha yoga in a sample of 97 individuals with MetS (77).

NATURAL REMEDIES FOR METABOLIC SYNDROME

The use of natural remedies may be an effective strategy for the treatment and prevention of MetS. Previous studies showed that different natural products may be used for these purposes. The results of many research articles should be confirmed.

Unsaturated fatty acids

Previous studies found the beneficial effect of unsaturated fatty acids on MetS. Lee and colleagues (78) reported that oral intake of encapsulated borage (*Borago officinalis* L.) oil in combination with echium (*Echium plantagineum* L.) oil may decrease low-density lipoprotein cholesterol (LDL-C) and total cholesterol, while encapsulated fish oil consumption may improve HDL-C and decrease hemoglobin A1c and triglycerides, studying a cohort of 59 individuals with MetS or T2D. Another study found the beneficial effect of the intake of encapsulated fish oil in combination with an energy-restricted diet on insulin and glucose levels and insulin resistance in a sample of 30 obese females with MetS (79). A research article by Venturini *et al.* (80) showed that the consumption of encapsulated ω-3 fish oil in combination with a diet enriched with extra virgin olive oil exerts antioxidant activity and ameliorates lipid profile in a sample of 102 individuals with MetS. Cicero and colleagues (81) reported the beneficial effect of dietary supplementation with PUFAs and red yeast rice on lipid profile in individuals with MetS and primary polygenic hypercholesterolemia. Another study found that the intake of skim

milk enriched with ω-3 PUFAs and oleate in combination with high-intensity aerobic training may ameliorate cardiometabolic health in a sample of 36 individuals with MetS (82). Tousoulis and colleagues (83) showed that encapsulated ω-3 PUFAs consumption improves cardiovascular health and lipid profile and exerts anti-inflammatory activity in a cohort of 29 individuals with MetS.

Artichoke

Previous studies reported that artichoke (*Cynara scolymus* L.) may be effective in the treatment of MetS. A research article found that the intake of artichoke leaf extract (ALE) may ameliorate cardiometabolic and NAFLD biomarkers in a sample of 100 individuals with MetS (84). Two previous studies showed the beneficial effect of ALE consumption on triglycerides in individuals with MetS (85, 86). Ebrahimi-Mameghani and colleagues (87) reported that oral intake of ALE may reduce insulin levels and insulin resistance in individuals with MetS. A research article by Rezazadeh *et al.* (88) found that ALE consumption may exert antioxidant activity, studying a sample of 68 individuals with MetS.

Resveratrol

Resveratrol is a natural polyphenol which exerts many health benefits. Previous research articles found that the intake of encapsulated resveratrol and δ-tocotrienol may ameliorate inflammatory, oxidative stress and cardiometabolic parameters (89) and MetS components through micro RNAs (miRNAs) modulation (90), studying samples of 82 participants with MetS. Chen and colleagues (91) reported that encapsulated resveratrol consumption exerts beneficial effects on the metabolism of lipids and glucose and insulin resistance in individuals with NAFLD. A previous study found that the intake of encapsulated resveratrol may ameliorate endothelial function in a sample of 30 overweight or obese individuals with mild insulin resistance and prediabetes (92).

Berberine

Berberine is a natural compound which has been studied in clinical trials related to MetS. Previous research articles reported the positive effect of the intake of berberine in combination with other compounds (i.e., monacolin K, policosanol, coenzyme Q10, folic acid and astaxanthin) on lipid profile and the risk of CVD in individuals with MetS (93, 94). Cicero and colleagues (95) found that the consumption of a nutraceutical combination containing tree turmeric (*Berberis aristata* DC.), banaba (*Lagerstroemia speciosa* L.), turmeric (*Curcuma longa* L.), folic acid, chromium picolinate and alpha-lipoic acid may ameliorate insulin resistance and lipid profile in a sample of 40 individuals with prediabetes. Another study showed the beneficial effects of the intake of berberine in combination with silymarin on cardiometabolic health in a cohort of 136 obese individuals with MetS and T2D (96).

Probiotics and prebiotics

Previous studies have reported the positive effect of probiotics and prebiotics on MetS. A research article by Rahimi *et al.* (97) found that the consumption of a synbiotic preparation may lower fasting blood glucose levels in a sample of 108 individuals with MetS. Another study reported the beneficial effect of the intake of a synbiotic preparation on insulin resistance, glucose and insulin levels, body mass index (BMI) and satiety in individuals with MetS following an energy-restricted diet (98). Tenorio-Jiménez and colleagues (99) showed that the intake of probiotics (*i.e.*, *Lactobacillus reuteri* V3401) may modify the gut microbiota and lower inflammation in a cohort of 53 participants with MetS following an energy-restricted diet in combination with physical activity. A previous study found that probiotics and prebiotics consumption has a beneficial effect on the prevalence of MetS and MetS components in a sample of 85 prediabetic participants (100).

Curcumin

Curcumin has many health-promoting properties and has been studied for its possible role

in the treatment of MetS. A previous study by Panahi *et al.* (101) found that oral intake of curcumin may have a beneficial effect on leptin and adiponectin levels in a cohort of 100 individuals with MetS. Di Pierro and colleagues (102) showed that curcumin consumption may be used in weight management programs, studying a sample of 44 overweight individuals with MetS. A research article found that oral intake of encapsulated turmeric in combination with black seeds (*Nigella sativa* L.) ameliorates MetS in a sample of 250 males with this condition (103). Bateni and colleagues (104) reported that the consumption of curcumin nanomicelle may lower triglyceride levels in individuals with MetS.

Garlic

Previous studies showed that garlic (*Allium sativum* L.) exerts beneficial effects on MetS. Matsumoto and colleagues (105) found that the intake of a garlic extract may improve cardiovascular health in a cohort of 55 individuals with MetS. A research article by Sangouni *et al.* (106) reported the positive effect of the consumption of a garlic supplement on MetS and NAFLD parameters, appetite and insulin resistance in participants with MetS. Another study found that the intake of a garlic supplement may ameliorate cardiometabolic health and gut transit time in a sample of 84 individuals with MetS (107).

Pomegranate

The benefits of pomegranate (*Punica granatum* L.) intake on MetS have been previously studied. Two research articles reported that oral intake of pomegranate juice exerts anti-inflammatory activity and has a beneficial effect on cardiovascular health in individuals with MetS (108, 109). A previous study by Esmaeilinezhad *et al.* (110) found that the consumption of synbiotic pomegranate juice may have beneficial effects on insulin levels, insulin resistance, body composition and weight management in a sample of 86 females with PCOS.

Olive polyphenols

Previous studies have shown the positive effect of olive polyphenols on MetS. A research article found that olive leaf polyphenols exert beneficial effects on glucose homeostasis in a sample of 45 overweight individuals (111). Sanchez-Rodriguez and colleagues (112) reported that olive oil with high polyphenolic content ameliorates parameters of endothelial function and MetS, studying a cohort of 51 participants. Two previous studies found the beneficial effects of extra virgin olive oil with high polyphenolic content on insulin resistance and glucose levels in healthy individuals (113) and on endothelial function in participants at risk of T2D (114).

CONCLUSIONS

This narrative review describes the role of diet, physical activity and natural remedies in the prevention and treatment of MetS. The Mediterranean diet, the energy-restricted Mediterranean diet and a diet characterized by high intake of healthy food have been shown to be effective in treating and preventing this condition. The fat-modified diet, the carbohydrate-modified diet, the high-protein diet, intermittent fasting and the plant-based diet are also promising strategies to consider for these purposes. Physical activity has been reported to be helpful for treating and preventing MetS, either alone or in combination with a proper diet and natural remedies. Unsaturated fatty acids, ALE, resveratrol, berberine, probiotics and prebiotics, curcumin, garlic, pomegranate and olive polyphenols are the natural remedies which have been previously studied for their beneficial effects on MetS. The results of many research articles reported in this review should be confirmed.

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ETHICS

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Conflict of interests
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Availability of data and material
Data and material are available on request from the Authors.

Authors' contributions
ADN, FG, FP and PZ conceived the study. ADN searched the scientific literature and wrote the initial draft of the manuscript. All Authors discussed the results and contributed to the final version of the manuscript. All Co-authors read and approved the final manuscript.

Ethical approval
N/A.

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