Review

Therapeutic potentials of natural products for post-traumatic stress disorder: A focus on epigenetics

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ABSTRACT

Post-traumatic stress disorder (PTSD) is a relatively common but complex mental illness with a range of diverse risk factors. Typical symptoms include the re-experience or avoidance of traumatic events, cognitive impairment, and hypervigilance. While the exact pathogenesis of PTSD is unclear, many studies indicate that epigenetic regulation plays a key role in its development. Specifically, numerous studies have indicated that the levels of histone acetylation and methylation, DNA methylation, and noncoding RNA are altered in PTSD patients. Further to this, natural products have been found to achieve epigenetic regulation of PTSD by regulating the expression of epigenetic enzymes, long noncoding RNA (lncRNA), and miRNA, thereby playing a role in improving PTSD symptoms. To date, however, no epigenetic regulation related drugs have been used in the treatment of PTSD. Furthermore, while natural products that can epigenetically regulate PTSD have received increasing levels of attention, there have not yet been any systematic reports on the topic. Here, we summarized the roles and mechanisms of natural products in the epigenetic regulation of PTSD, providing a novel and unique perspective that will help to guide the development and application of new PTSD treatments.

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Contents

1. Introduction

Post-traumatic stress disorder (PTSD) is both a psychiatric and psychological disease that persists after individuals have experi- enced a severe trauma, stimulation, or death threat (Pitman et al., 2012; Schoner, Heinz, Endres, Gertz, & Kronenberg, 2017). The core symptoms are the re-experience or avoidance of trau- matic events, decreased fear memory extinction, cognitive impair- ment, and hypervigilance (Shalev, Liberzon, & Marmar, 2017; Yabuki & Fukunaga, 2019), which can further result in experiences of agony or disturbance. The incidence of PTSD is also associated with an individuals' social background, personal experience, and

sex; for example, the prevalence of PTSD in women is twice that in men (Yehuda et al., 2015). More than 70 % of people worldwide have reportedly suffered from a traumatic experience (Benjet et al., 2016), and some of these people will eventually develop PTSD, and perhaps even lifetime PTSD, the prevalence of which is approximately 3.9 % (Watson, 2019).

Individuals who have personally experienced a traumatic event such as fire, war, earthquake, motor vehicle accident, sex intrusion, child maltreatment, or terrorist attack are more likely to develop PTSD (Liriano, Hatten, & Schwartz, 2019). However, people who have suffered major traumatic events indirectly or as witnesses may also be affected by these traumas, such as frontline police officers, firefighters, or those involved in earthquake rescues. Some studies have shown that in addition to the aforementioned factors, direct severe trauma can induce PTSD, and childhood adversity and psychiatric history may also increase the risk of its development (Watson, 2019). Medical comorbidities may also lead to a higher probability of developing PTSD, such as inflammation, cardiovascular disease, or coronavirus disease 2019 (COVID-19) (Edmondson & von Kanel, 2017; Hori & Kim, 2019; Tarsitani et al., 2021). Related research has shown that the risk factors for PTSD are always present, before, during, and after the trauma, such as low social status and poor social support, severity of trauma, and post-traumatic unemployment (Maes, Delmeire, Mylle, & Altamura, 2001). Moreover, some patients may choose to self-harm or commit suicide in the worst situations, which decreases quality of life for both the patients and their caregivers, thereby putting a huge burden on the social economy and those providing medical care (Watson, 2019). In summary, PTSD is complicated as it has many triggers and symptoms; furthermore, patients with PTSD may not show any symptoms if they do not experience triggering events or places, and this phenomenon increases the difficulty of developing effective treatments.

Animal and clinical studies have reported the presence of specific neural circuits, functional structures, hormones, and other neurobiological systems that are associated with the pathophysiological basis of PTSD; however, the underlying pathogenesis is still unclear. Pathophysiological abnormalities of the disease mainly include the dysregulation of the hypothalamus–pituitary–adrenal (HPA) axis, increased inflammation, abnormal release of neurotransmitters, reduced neurogenesis, abnormal apoptosis, and autophagy processes. PTSD is regarded as a very complex psychiatric disease, as its onset involves different brain areas including the peripheral and central regions, which limits our understanding of an exact cause, and thus further research is required.

Recently, PTSD was recognized as a global public health concern (Watson, 2019); making the development of effective treatments a priority for medical research. Current methods to treat PTSD include psychotherapy and pharmacotherapy, however, chemical and Chinese medicine-based therapies have also been incorporated into pharmacotherapy strategies. Numerous articles investigating the effects of chemical medicines and natural products for the treatment of PTSD have been published, as well as several studies investigating the effects of epigenetics on PTSD. Moreover, there are several related articles available on natural products that can reportedly be used to treat PTSD; however, there are no reports that natural products modulate PTSD from an epigenetic perspective. This review aims to outline the effects of natural products on epigenetic regulations in PTSD, with an emphasis on their epigenetic regulation mechanisms.

2. Role of epigenetics in PTSD

PTSD is a complicated syndrome caused by multiple factors, including related traumatic events, the external environment, and genetics. In the traditional sense, heredity refers to patient characteristics that are reflected in their offspring. At the molecular level, heredity is the transmission of DNA-encoded genetic information from parents to their offspring through meiosis (Daskalakis, Rijal, King, Huckins, & Ressler, 2018). There is also a theory of epigenetics, which was originally proposed by Waddington (Martinez Fernandez, 1959). The epigenetic mechanism describes the encoding of biochemical information obtained from an individual's experience and environment into the genomic structure of each cell, thereby affecting and regulating subsequent gene regulation and expression, cell function and phenotype, and ultimately, individual performance (Kim, Smith, Nievergelt, & Uddin, 2018). In this process, the epigenome plays an important role that cannot be ignored. The epigenome adapts to environmental influences in the form of chemical and protein modifications to the chromatin made up of DNA, proteins, and RNA (Daskalakis, Rijal, King, Huckins, & Ressler, 2018), thereby providing the genome with continuous regulatory feedback caused by environmental changes (Kim, Smith, Nievergelt, & Uddin, 2018). An epigenetic perspective states that both the environment and genes interact to regulate PTSD (Howie, Rijal, & Ressler, 2019). Furthermore, epigenetic regulations create central regulatory mechanisms in such interactions. As the name suggests, epigenetic regulation functions as environmental changes are "written" into the genome, thus mediating alterations in gene expression, rather than directly changing the coding sequence (Howie, Rijal, & Ressler, 2019; Zannas, Provencal, & Binder, 2015). Epigenetics is linked to PTSD, as to a certain extent, it can mediate changes in brain function and the gene expression of related nerves caused by the external environment or trauma exposure (Zannas, Provencal, & Binder, 2015). There are three main mechanisms of epigenetic regulation: histone modification, DNA modification, and noncoding RNA (Hwang, Aromolaran, & Zukin, 2017). These three factors are not independent in the regulation of PTSD, but are interrelated and influence each other. For example, histone methylation, acetylation, DNA methylation, and non-coding RNA can all play a role in neurogenesis (Yao et al., 2016).

Medicinal plants are often ancient and have commonly been used as medicines for thousands of years in multiple countries (Marrelli, 2021). According to previous reports, traditional medicinal plants have been found to have more or less therapeutic or preventive effects on a variety of neurological diseases, such as neuropsychiatric and neurodegenerative diseases (Luthra & Roy, 2022; Rauf & Rahman, 2022). For example, ginseng, *Withania somnifera* (L.) Dunal, *Bacopa monnieri* (L.) Wettst, and *Ginkgo biloba* L. are medicinal plants that are commonly used to prevent neurological symptoms (Luthra & Roy, 2022). While natural products can be sourced from a variety of plants, animals, microorganisms, and minerals, those used for medicinal purposes are often derived from plants and are usually characterized as having a low toxicity and general benefits to human health (Gunesch et al., 2020). Medicinal plants are an important source of a wide variety of bioactive chemicals that contribute to the development of increasingly efficient multi-target drugs (Marrelli, 2021). Some natural products, such as gastrodin (GAS), are also reportedly effective at protecting nerves (Dash et al., 2021). Consequently, they are often used to treat or prevent neurological disorders such as PTSD, depression, and neurodegenerative diseases. Some studies indicate that mangiferin can exert neuroprotective effects by activating Nrf2 downstream genes (Li et al., 2020). In addition, it has also been discovered that water extracts obtained from *Cymbopogon citratus* (D.C.) Stapf can also alleviate the occurrence of neurological diseases (Umukoro, Ben-Azu, Ajayi, Adebesin, & Emokpae, 2020). In conclusion, the use of natural products is now in its golden age, and holds great promise for epigenetic drug development and discovery, and some natural epigenetic modulators have recently

been used in clinical studies. Natural products are currently more widely used to treat cancer tumors, but this may be in part because there have been relatively few studies on neurological diseases, such as PTSD. Therefore, the use of natural products as an entry point for more in-depth research into PTSD will aid in the development of new drugs and treatments for PTSD. The epigenetic regulatory mechanisms of common natural products for the treatment of PTSD are summarized in Fig. 1.

2.1. Histone modification

Histones are basic proteins present in chromatin that bind to DNA (Huang & Bonner, 1962), and usually consist of five components, H1, H2A, H2B, H3, and H4. Histone proteins bind to DNA to form chromatin, which can then also be interpreted as a repetition unit consisting of nucleosomes, a single nucleosome consisting of a core octomer, a 147-bp length DNA fragment, and a monomer histone H1. In addition, the core octamer is composed of two H2A, H2B, H3, and H4 monomers (Luger, Mader, Richmond, Sargent, & Richmond, 1997). The nucleosomes are mainly connected by 50-bp splice DNA, the site of the connection is the monomer histone H1 on the nucleosome (Wu et al., 2022), and the nucleosomes are closely connected to form the so-called chromosome. In general, nucleosomes hinder DNA transcription, but the presence of histones can affect the conformation and activity of chromatin through post-translational modifications (Lawrence, Daujat, & Schneider, 2016), thus altering gene transcription, DNA replication, repair, recombination, and other processes (Wu et al., 2022).

Histone modifications regulate alterations in gene expression, primarily by affecting the structure of chromatin. The main mechanisms by which histones are modified are as follows: acetylation, methylation, phosphorylation, and ubiquitination (Howie, Rijal, & Ressler, 2019; Strahl & Allis, 2000), SUMOylation, ADP ribosylation,

and deamination (Kouzarides, 2007). Of the histone modifications listed, histone acetylation is the most widely studied, and has a basic effect on the processes of transcriptional regulation (Strahl & Allis, 2000; Struhl, 1998; Zannas, Provencal, & Binder, 2015). In addition to acetylation, there have been numerous studies on the regulation of diseases by natural products through the epigenetic mechanisms of histone methylation, but relatively few studies on histone phosphorylation and ubiquitination.

It is widely acknowledged that PTSD is caused in part by a memory association, known as memory impairment, and that histone modifications can regulate the transcription and translation processes required for memory. For example, histone acetylation represents the formation of memory (Levenson et al., 2004), and when it is blocked or inhibited, this may lead to episodic fear memory disorders and long-term memory deficits (Sillivan, Vaissiere, & Miller, 2015). Therefore, starting from the point of histone modification, it is more conducive for us to understand the pathogenesis of PTSD, and further facilitate the association of natural products that play a therapeutic role through histone modification with PTSD, to understand the treatment and prevention of PTSD from a new perspective.

2.1.1. Histone acetylation

Histone acetylation involves the addition of acetyl groups to the lysine residues at the N-terminus of histones, a process catalyzed by histone acetyltransferases (HATs). This process weakens the binding of histones to DNA, forming a decondensed chromatin structure that is more likely to facilitate transcription. In contrast, histone deacetylation is catalyzed by histone deacetylases (HDACs) and can inhibit gene expression (Graff & Tsai, 2013; Zannas, Provencal, & Binder, 2015).

The role of epigenetic regulation in neurodevelopment has been confirmed in several different studies, and the results indicate that histone acetylation is associated with memory and cognition (Peixoto & Abel, 2013; Starr, 2019). For example, increased histone H3 acetylation was found to promote long-term memory formation (Takei et al., 2011). Animal experiments have also shown that histone acetylation levels are reduced in animals with PTSD-like symptoms (Alzoubi, Al Subeh, & Khabour, 2019). One animal study that examined the HDAC2, H3K9ac, and brain-derived neurotrophic factor (BDNF) contents found the same results as in previous BDNF-related studies, in that the level of BDNF was reduced in PTSD. However, the study also found that a reduction in BDNF levels was associated with a reduction in H3K9ac expression, and this was mainly reflected by reduced acetylation of histone H3 at the BDNF promoter, leading to lower BDNF expression, and this promoted the development of PTSD (Alzoubi, Al Subeh, & Khabour, 2019). Histone acetylation levels are thought to affect synaptic plasticity, which in turn affects some behaviors associated with PTSD, such as depression-like behaviors (Sun et al., 2021). Furthermore, HDAC inhibitors have been found to enhance fear extinction and ameliorate PTSD symptoms. An experiment using rats showed that the HDAC inhibitor vorinostat, which blocked the activity of HDAC, could enhance the levels of histone acetylation in the hippocampus by increasing the expression of histones H3 and H4 at the promoter of the NR2B genes in rats with PTSD, and thus exert a certain therapeutic effect (Matsumoto et al., 2013). These results are consistent with the conclusion that histone acetylation levels are reduced in patients with PTSD (Alzoubi, Al Subeh, & Khabour, 2019; Matsumoto et al., 2013). Some additional traits associated with histone acetylation are listed in Table 1.

Most natural products are extracted from medicinal plants, and they affect various diseases in different ways. For example, natural products can alleviate or worsen the occurrence or development of cancer by targeting a variety of genetic or epigenetic changes
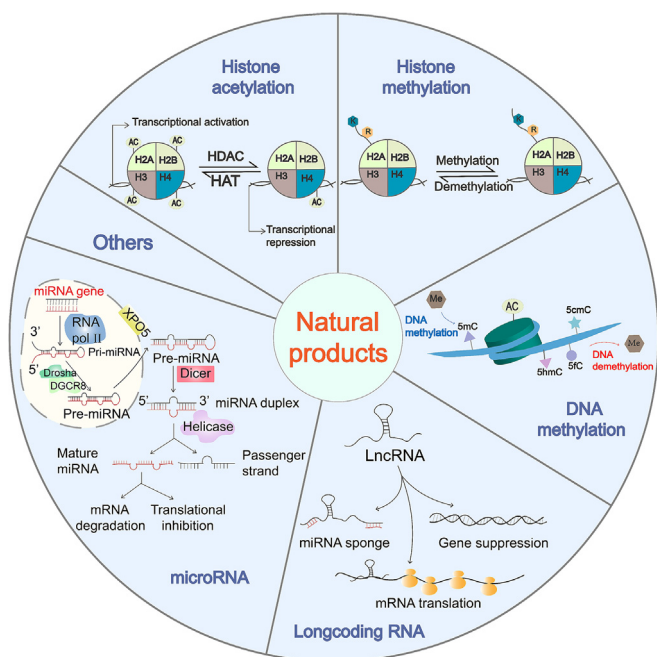
Fig. 1. Therapeutic mechanisms of natural products for PTSD. Natural products can exert epigenetic regulatory effects through histone acetylation, histone methylation, DNA methylation, miRNA, LncRNA, and other therapeutic mechanisms. In addition, abnormal histone acetylation or methylation levels and abnormal gene expression levels can also be rescued through the epigenetic effects of natural products, thus playing a therapeutic role.

Table 1
Preclinical studies investigating role of histone acetylation in PTSD.

Disease	Cases	Markers	Main results	Main mechanisms	References
Preclinical studies	Control (M, n = 12; F, n = 12)PTSD (M, n = 10; F, n = 10)MS3h-PTSD (M, n = 10; F, n = 10)MS6h-PTSD (M, n = 10; F, n = 10)	Western blotting HDAC2 H3K9ac	PTSD vs control: ↑HDAC2 protein and mRNA expression in HIP ↓H3K9ac protein in HIP	HDAC	Sun et al., 2021
	SPS + DMSO (n = 10) SPS + Vorinostat (n = 10)	Western blotting Ac-H3 Ac-H4	Vorinostat vs DMSO: ↑Ac-H3 and Ac-H4 in HIP	HDAC	Matsumoto et al., 2013
	Control (n = 4–5) ELS ELS + EE	ELISA Western blotting Ac-H3K9 Ac-H4K12	ELS vs ELS + EE: ↓Ac-H3K9 and Ac-H4K12 in Hip ↓HAT in Hip ↑HDAC in AMY	HAT HDAC	Xu et al., 2022

Note:[a] ↓decreased, ↑ increased. [b] Abbreviations: M, male; F, female; ac, acetylation; EE, environmental enrichment; ELS, early life stress; me, methylation; MS, maternal separation.

(Huang et al., 2016). Numerous reviews have shown that natural products, such as rosmarinic acid (RA), tetramethylpyrazine (TMP), oleuropein (OLE), *trans*-resveratrol (*trans*-RE), genistein (GEN), and curcumin (CUR) can regulate the occurrence of different diseases or exert therapeutic effects by affecting the levels of histone acetylation or HDAC activity.

For example, studies have shown that RA can inhibit the expression of HDAC2 in animals, while HDAC inhibition can alter apoptotic gene changes and produce pro-apoptotic effects (Jang, Hwang, & Choi, 2018). It has also been reported that RA can promote hippocampal cell proliferation and improve PTSD-like symptoms (Nie et al., 2014). It was thus hypothesized that RA may influence some hippocampal genes, such as those related to inflammation, cell proliferation or autophagy, and apoptosis, through epigenetic mechanisms such as the inhibition of HDAC, leading to changes in animal behavior. TMP and OLE also have similar inhibitory effects on HDAC as the RA. TMP is extracted from a Chinese herbal medicine called *Ligusticum chuanxiong* Hort., which have functions to promote neurogenesis, and specifically, the differentiation of neural stem cells into neurons during neurogenesis. It was also found that TMP may change the structure of the topoisomerase IIβ (TopIIβ) gene through its HDAC inhibition effects, increasing the acetylation of histones H3 and H4 near the TopIIβ promoter region, promoting the transcription of topoisomerase IIβ gene, and promoting neurogenesis (Yan et al., 2014). For OLE, the same is true as it inhibits HDAC and promotes histone H3H4 acetylation, thus reversing the memory and cognitive impairment caused by HDAC overexpression due to disease (Luccarini et al., 2015). For histone deacetylases, *trans*-RE also has a regulatory effect. Resveratrol exists in both formal and *trans*-isomer forms, of which only the latter shows biological activity, primarily as an anti-inflammatory, antioxidant, and antitumor agent (Dutt, Gupta, Dabur, Injeti, & Mittal, 2015). Studies have found that *trans*-RE can downregulate the expression of proinflammatory factors, such as interleukin-1β and interleukin-6 by increasing the activity of sirtuin 1 (SIRT1), and can also exert anti-inflammatory and neuroprotective effects by regulating the expression of miRNA (Dutt et al., 2015; Isac et al., 2017).

In addition to natural products acting on HDAC, GEN and CUR can also regulate histone acetylation levels by altering the expression of HAT (Majid et al., 2008; Yan et al., 2017). For example, it was found that when GEN was used to treat tumors, it could induce the transcriptional activation of tumor suppressor genes and change gene expression by upregulating HAT, and then catalyze the acetylation of histones H3 and H4 near the transcription start sites of p21, p16, and other tumor suppressors, thus achieving certain anti-tumor effects (Majid et al., 2008). In contrast, CUR, as a natural HAT inhibitor, could reduce H3K9 acetylation by inhibiting the expression of HAT, and then downregulating the expression of apoptosis-related genes, such as Caspase-3, to promote apoptosis and maintain the normal operation of organs and tissues (Yan et al., 2017). Combined with the epigenetic regulation mechanisms of the natural products mentioned above, we have hypothesized that changing the histone acetylation levels of certain gene loci may alleviate the symptoms of PTSD patients to some extent in the PTSD model. Hence, natural products with HDAC and HAT regulation may improve PTSD-like symptoms and provide a new safe option for future patient treatments. The histone acetylation sites of natural products are summarized in Fig. 2, and some common natural products that may be used to treat PTSD by regulating histone acetylation are summarized in Table 2.

2.1.2. Histone methylation

Histone methylation, which were first discovered in the 1960s (Murray, 1964), is another epigenetic regulatory mechanism and is distinct from histone acetylation. Histone methylation can occur at different sites on the histones, but the main sites of action include lysine residues and arginine residues (Jambhekar, Dhall, & Shi, 2019). The methylation process requires the assistance of histone methyltransferases (HMTs) such as lysine methyltransferases (KMTs) or protein arginine methyltransferases (PRMTs) to transfer methyl groups to the lysine or arginine residues of histones (Howie, Rijal, & Ressler, 2019; Li, Xiao, & Chen, 2022). When histone amino residues bind to methyl groups, chromatin relaxes, which facilitates gene expression. Conversely, histone demethylation inhibits transcription, a process catalyzed by histone demethylases (HMDs). However, different methylation and demethylation sites have different functions. For example, H3K4me3 serves as a marker for promoting transcription (Barski et al., 2007), while H3K9me3 represents gene silencing and heterochromatin (Bannister et al., 2001; Barski et al., 2007). Hence histone methylation is a complicated process. Moreover, it plays an imperative role in the development and treatment of psychiatric diseases (Li et al., 2019; Peter & Akbarian, 2011). Histone methylation alters BDNF levels, thereby changing brain function and neuronal development. A study observed a trend of increasing BDNF with a decrease in H3K9me2 following the administration of Unc0642, which was found to work by inhibiting an enzyme called EHMT2 (histone methyltransferase). The process promoted the transcription and expression of BDNF-related mRNA and proteins by reducing H3K9me2 at the BDNF promoter in the hippocampus and prefrontal cortex (Zhao et al., 2020). However, histone methylation was also connected with inflammation. For instance, the association among histone methylation, wingless (WNT) signaling,
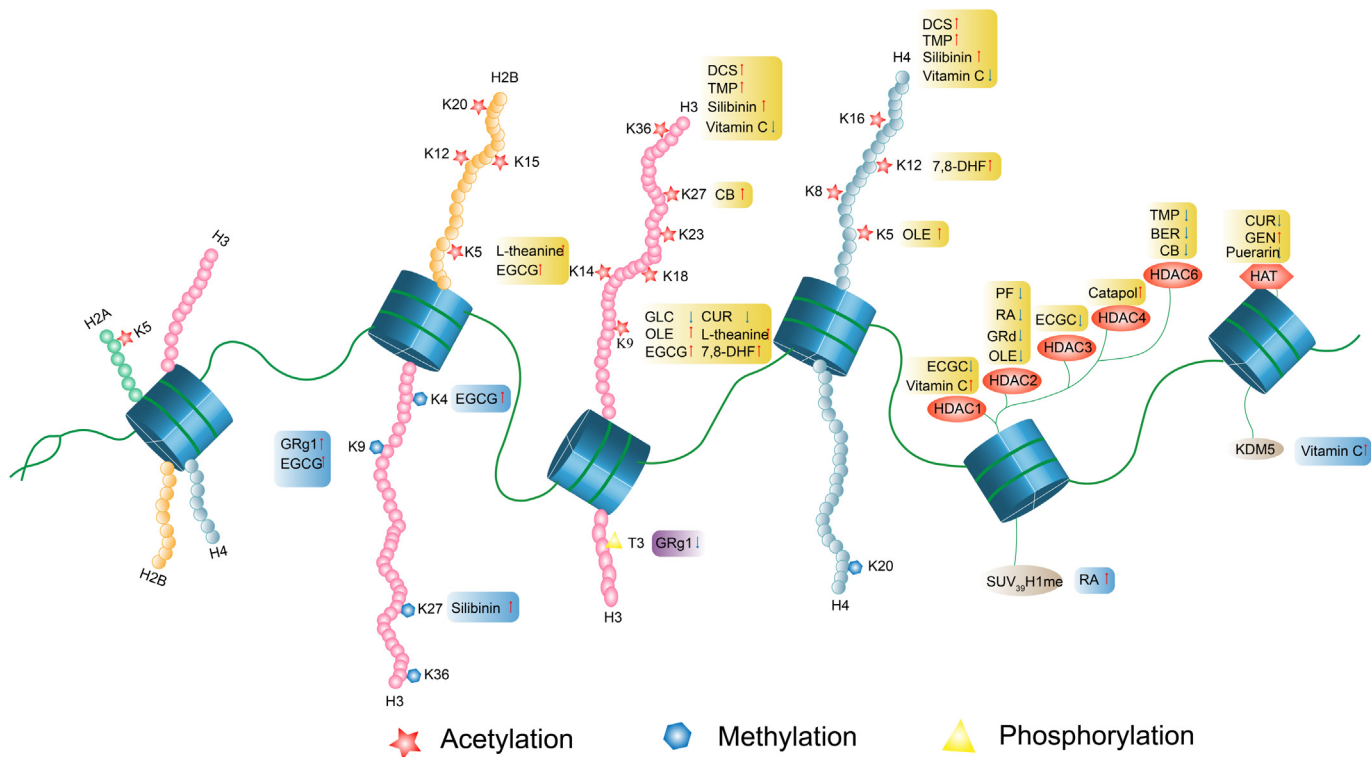
Fig. 2. Effects of various natural products on histone acetylation and methylation in PTSD. Histone modification mainly includes histone acetylation, methylation and phosphorylation. Firstly, for histone acetylation, the modification site is mainly at the relatively conserved lysine site of the N terminal of histone, and the process is mainly coordinated by histone acetyltransferase and histone deacetylase. Secondly, the main modification sites of histone methylation are arginine and lysine. In addition, different modifications at different sites also play different effects on transcription and gene expression. Moreover, natural products can exert therapeutic effects by acting on different sites. For example, EGCG can up-regulate the methylation level of H3K27 site and also up-regulate the acetylation level of H3K9 site. In short, different natural products can play different regulatory roles by acting on different sites.

Table 2
Common natural products that can be used to regulate histone acetylation in PTSD.

Chemicals	Main results	References
RA	↓HDAC2	Jang, Hwang, & Choi, 2018
Catalpol	↑HDAC4	Zou, Zhong, Wu, Wang, & Liu, 2019
	↑SIRT1	
GRd	↓HDAC2	Wan et al., 2017
PF	↓HDAC2	Liu, Zhang, Wu, & Feng, 2022; Zhang et al., 2018
trans-RE	↑SIRT1	Dutt et al., 2015
CUR	↓HAT	Montagud-Romero et al., 2016
	↓H3K9ac	
Puerarin	↓HAT	Han et al., 2015
EGCG	↑H3K9/14ac and H3ac	Ciesielski, Biesiekierska, & Balcerczyk, 2020; Pan et al., 2017
	↓HDAC1 and HDAC3	
Silibinin	↓HDAC activity	Mateen et al., 2012
	↑H3ac and H4ac	
GEN	↑HAT expression	Li, Liu, Andrews, & Tollefsbol, 2009
OLE	↑H3K9 and H4K5	Luccarini et al., 2015
	↓HDAC2	
7,8-DHF	↑H3K9ac and H4K12ac	Zeng et al., 2011
GLC	↓H3K9ac	Thakur, Sadanandan, & Chattopadhyay, 2020
Vitamin C	↓H4ac and H3ac	Mustafi et al., 2019
	↑HDAC1	
TMP	↑H3ac and H4ac	Yan et al., 2014
	↓HDAC	
L-theanine	↑H3K9ac and H3K14ac	Kikuchi et al., 2022
BER	↓HDAC	Kalaiarasi et al., 2016
CB	↑H3K27ac	Scherma et al., 2020
	↓HDAC6	
DCS	↑H3ac and H4ac	Wang et al., 2012

Note: [a] ↓ decreased, ↑ increased. [b] Abbreviations: BER, berberine; CB, cannabinoids; CUR, curcumin; DCS: D-Cycloserine, EGCG, epigallocatechin gallate; GEN, genistein; GLC, glycyrrhizin; GRb1, ginsenoside Rb1; GRd, ginsenoside Rd; HAT, histone acetyltransferase; HDAC, histone deacetylase; OLE, oleuropein; PF, paeoniflorin; RA, rosmarinic acid; SIRT1, sirtuin 1; TMP, tetramethylpyrazine; trans-RE: trans-resveratrol. 7,8-DHF, 7,8-dihydroxyflavone.

and inflammatory cytokines such as interleukins and interferons has been demonstrated in a series of preclinical experiments, and studies have found that the addition of H3K9me3, H3K4me3, and H3K36me3 expression led to the elevation of IL-12, further augmenting inflammation in patients with PTSD (Bam et al., 2020; Bam et al., 2016). Specifically, the overexpression of wingless 10b (WNT10B) is associated with the high expression of histone H3K4me3 around the WNT10B promoter. That is, WNT signaling regulates histone methylation by affecting HMD, which in turn regulates the expression of inflammatory cytokine genes, such as interferon-γ (INF-γ) and IL-12, and results in the level of inflammation detected in people with PTSD (Bam et al., 2020). Overall, understanding histone methylation will contribute to a deeper understanding of the pathogenesis of PTSD.

Current research on PTSD and histone modifications has predominantly focused on the above two protein modification methods, and data relating to histone phosphorylation and ubiquitination is currently lacking. However, epigenetic studies on PTSD are still rare, and most attention has been focused on inflammation and BDNF in both preclinical and clinical trials. Moreover, data has shown that histone modification-related enzymes, such as HDAC or HMT, always play a major role during the process of histone modification. Many drugs or natural products may affect discrepant modification sites by regulating different enzymes (Bam et al., 2020; Zhao et al., 2020). In conclusion, only BDNF and inflammation were involved in the above two aspects, yet we can speculate that multiple pathophysiologies involved in the pathogenesis of PTSD may be regulated by epigenetic mechanisms. Furthermore, the specific regulatory mechanisms are not yet fully understood. The histone methylation sites of natural products are summarized in Fig. 2. A summary of current preclinical and clinical trials associated with histone methylation is provided in Table 3.

Although most of the relevant studies on histone methylation are related to cancer, there are some reports on the role of histone methylation in neuropathic diseases, including learning, memory, and neuroinflammation. A large number of animal experiments and clinical studies have shown that histone methylation levels in PTSD patients show an upward trend, and the enhanced methylation of some histones is associated with BDNF and inflammation levels (Bam et al., 2016; Zhao et al., 2020). By reviewing the abundance of available literature, some natural products were also found to affect the methylation levels of histones, such as silibinin, epigallocatechin gallate (EGCG), ginsenoside g1 (GRg1), and extracted vitamin C. For example, silibinin and EGCG are both HDAC inhibitors, but both also regulate histone methylation. Silibinin can increase the level of H3K27me3, which has an inhibitory effect on transcription, and EGCG can increase the methylation level of several sites, including H3K4me3 (promoting transcription) and H3K9me3 (inhibiting transcription), and extracted vitamin C, which is discussed later, has a similar effect (Anestopoulos et al., 2016; Ciesielski, Biesiekierska, & Balcerczyk, 2020; Coker, Smith-Diaz, Dyson, Vissers, & Berry, 2022). Silibinin can not only interfere with histone modifications, but also improves DNA methyltransferase (DNMT) activity. Linking the effects that silibinin has on anxiety and depression and reducing fear behavior with its effects on increasing H3K27me3, we have proposed that it may inhibit transcription by increasing H3K27 trimethylation at promoters or other loci of genes related to PTSD symptoms, and thus improve disease symptoms (Anestopoulos et al., 2016). Similarly, some studies suggested that EGCG alleviated PTSD mainly by inhibiting neuroinflammation. EGCG can affect the methylation of multiple histone sites, among which H3K9me3 is a transcriptional repressor. Therefore, EGCG may increase the histone H3K9me3 of the inflammatory cytokine gene, and then suppress the expression of inflammatory cytokines, producing anti-inflammatory effects and alleviating PTSD symptoms (Ciesielski et al., 2020). However, the connection between the two has not yet been fully elucidated.

GRg1 also promotes H3K9 methylation, and can regulate noncoding RNA (Kwok et al., 2017). Extracted vitamin C was also found to have epigenetic regulatory effects, such as increasing lysine demethylases (KDM) activity and mediating histone demethylation (Coker, Smith-Diaz, Dyson, Vissers, & Berry, 2022). However, there is limited information available regarding their regulatory effects on histone methylation, and their precise mechanisms must be elucidated in future studies.

Furthermore, we have found that some natural products can also affect BDNF levels and related inflammatory factors in PTSD patients; for example, GRg1 can increase BDNF while EGCG can reduce interleukin 1β (IL-1β) and tumor necrosis factor-α (TNF-α) in the hippocampus (Lee et al., 2016; Lee, Shim, Lee, & Hahm, 2018). However, the exact histone modification mechanisms of these natural products in relation to PTSD is not well understood, and further research is required to address this. Other types of histone modification, such as phosphorylation and ubiquitination also require further investigation. The histone methylation sites of several common natural products and the different site modifications are described in Fig. 2. In addition, this review has provided a summary of natural products that can regulate histone changes through epigenetic regulation, such as histone methylation in Table 4.

Table 3
Preclinical and clinical studies investigating role of histone methylation in PTSD.

Diseases	Cases	Markers	Main results	Main mechanisms	References
Preclinical studies	Adolescent control (n = 12)Adult control (n = 12)Adolescent PTSD (n = 12)Adult PTSD (n = 12) Adolescent PTSD + Unc0642 (n = 12) Adult PTSD + Unc0642 (n = 12)	Western blotting H3K9me2	PTSD vs Control: ↑H3K9me2 expression in HIP and PFC	EHMT2	Zhao et al., 2020
Clinical studies	Control (n = 6)PTSD (n = 6)	H3K4me3	PTSD vs Control: ↑H3K4me3 around promoter region of WNT10B, WNT10A, WNT7A, DVL1 and TCF7	HMD	Bam et al., 2020
	Control (n = 17)PTSD (n = 16)	ChIP-seq H3K4me3 H3K27me3 H3K36me3 H3K9me3	PTSD vs Control: ↑H3K4me3, H3K36me3 and H3K9me3 ↔H3K27me3	KDM5B	Bam et al., 2016

Note: [a] ↓ decreased, ↑ increased, ↔ unchanged. [b] Abbreviations: ac, acetylation; ChIP-seq, chromatin immunoprecipitation sequence; DMSO, dimethyl sulfoxide; EE, environmental enrichment; ELS, early life stress; me, methylation; KDM5B, lysine demethylase 5B; MS, maternal separation.

Table 4
Common natural products that can regulate histone methylation.

Chemicals	Epigenetic regulation	References
RA	↑SUV$_{39}$H1	Lee, Park, & Han, 2021
GRg1	↑H3K9me	Gao et al., 2020
EGCG	↑H3K4me3 and H3K9me3	Ciesielski et al., 2020
Silibinin	↑H3K27me3	Anestopoulos et al., 2016
Vitamin C	↑KDM5B	Coker, Smith-Diaz, Dyson, Vissers, & Berry, 2022

Note: [a] ↓ decreased, ↑ increased. [b] Abbreviations: EGCG, epigallocatechin gallate; GRg1, ginsenoside Rg1; RA, rosmarinic acid.

2.2. DNA methylation

In recent decades, epigenetic mechanisms have received increasing attention in relation to neurological diseases. In addition, recent studies have shown that DNA methylation is associated with the development of diseases and clinical symptoms. Due to its reversible nature, DNA methylation has become a hot and valuable target for therapeutics or interventions (Jones, Ohtani, Chakravarthy, & De Carvalho, 2019). DNA methylation is a kind of epigenetic mark that directly modifies DNA (Younesian, Yousefi, Momeny, Ghaffari, & Bashash, 2022), and this process is mainly involved in gene expression via the recruitment of proteins that participate in the inhibition of DNA binding with transcription factors and the inhibition of genes to further regulate gene function, thus affecting normal neurodevelopment (Moore, Le, & Fan, 2013). DNA methylation is the process of adding a methyl group to the C5 position of cytosine, which is mediated by DNA methyltransferases (DNMTs) and DNA demethylases, and is associated with gene silencing (Morrison, Miller, Logue, Assef, & Wolf, 2019).

DNA methylation, in addition to being widely studied in relation to cancer, has also been a focus of neurological research, including PTSD. A previous study found that differential expression of methylation in some regions can be detected in PTSD. For example, a clinical study found two differentially methylated regions (DMR) in PTSD, *HLA-APB1* and *SPATC1L*, and the degree of methylation in these regions could be used to assess the risk of PTSD (Katrinli et al., 2021). In addition to the above DMRs, the methylation level of some loci was found to be abnormal in PTSD. For example, spindle and kinetochore-associated protein 2 (SKA2) methylation is often used as a marker for assessing suicide risk. An analysis of blood samples from more than 200 veterans found that the methylation levels of the *SKA2* gene affect the thickness of the brain's prefrontal cortex and correlate with the severity of PTSD symptoms (Sadeh et al., 2016). These data provide a basis by which to evaluate the severity of PTSD.

Numerous studies have also been conducted to determine which PTSD symptoms can be affected by DNA methylation, and a reciprocal relationship between DNA methylation and cognition and inflammation was identified. For example, klotho (KL) methylation has been used as a predictor of inflammation. By measuring the KL DNA methylation level in PTSD patients, it was found that the more severe the PTSD symptoms, the higher the DNA methylation level and the lower the KL gene expression. Conversely, the levels of related inflammatory markers such as C-reactive protein (CRP) tended to increase (Wolf et al., 2020). This, in turn, leads to aggravated inflammation, and the patient's cognition is also damaged to a certain extent. In addition to KL gene methylation being associated with inflammation, absent in melanoma 2 (AIM2) gene methylation also affects inflammation, and Mc et al. (Mc et al., 2021) and Hawn et al. (Hawn et al., 2022) found that *AIM2* gene methylation could affect the content of CRP and other inflammatory factors *in vivo*, and indicated that there was a certain relation-

ship between PTSD and AIM2 methylation. In addition, DNA methylation is known to be active in the development and maturation of the central nervous system, so external stimuli or stress may induce changes in gene methylation in the central nervous system. Among them, BDNF is common and is associated with cognitive impairment in patients. Abnormal methylation of the hippocampal *BDNF* gene is also found to be a major cause of hippocampal dysfunction in PTSD patients, as DNA methylation of the *BDNF* gene can reduce BDNF expression, resulting in cognitive deficits in patients (Roth, Zoladz, Sweatt, & Diamond, 2011). Apart from the previously described association of DNA methylation with PTSD symptoms, such as cognitive impairment and increased inflammation, DNA methylation and DNA demethylation have also been connected with fear extinction, and this correlation is also related to the activation of neurons in various regions of the brain (Shan, Guo, van den Heuvel, van Heerikhuize, & Homberg, 2018). As for DNA methylation and demethylation, previous studies have shown that abnormal methylation and methylation-related enzymes such as DNMT often cause deficient fear memory and impaired fear extinction. For example, when DNMT is inhibited, the decrease of 5-mc expression can promote high expression levels of related genes, and then interfere with the consolidation phase of fear memory (Shan, Guo, van den Heuvel, van Heerikhuize, & Homberg, 2018). Although impaired fear extinction is not completely regulated by DNA methylation/demethylation, it can be concluded that they influence fear behavior in PTSD mice to some extent. The remaining experiments are summarized in Table 5.

In summary, genes with abnormal DNA methylation were found to possibly play a role in the development of PTSD, but whether these genes directly contribute to the onset or persistence of PTSD is not currently known. However, it is promising that we can understand the pathogenesis and related pathological changes of PTSD from the perspective of epigenetics. In addition, the effects of DNA methylation on PTSD are multifaceted, and the effects of DNA methylation may be passed on from parents to offspring. Therefore, further molecular studies of PTSD will help to elucidate the pathogenesis of PTSD.

In addition to histone modifications, numerous lines of evidence support the important role of DNA methylation in PTSD, which can be regulated by DNA methylation-related enzymes. The modification sites for DNA methylation in several common natural products and their different modifications are summarized in Fig. 3. The role of natural products in PTSD from the perspective of DNA methylation was reviewed. While some natural products were found to interfere with DNA methylation levels, their effects on PTSD have not yet been reported. Here, a summary of the natural products that can be used to treat PTSD and the changes in the epigenetic regulations is provided. Epigenetic regulations in PTSD affect the immune system as well as the stress response system (Morrison, Miller, Logue, Assef, & Wolf, 2019). Lycopene, EGCG, extracted vitamin C, vitamin E, and curcumin are known to improve PTSD symptoms by regulating DNA methylation. For example, lycopene, an extract with anti-inflammation and antioxidation effects, has been implicated in the pathogenesis of various diseases such as PTSD, and it can thus be used to treat a diverse array of disorders. Studies have also found that in addition to enhancing the level of DNA methylation (King-Batoon, Leszczynska, & Klein, 2008), lycopene can also reduce the expression of inflammatory factors, such as interleukin 6 (IL-6), IL-1β, and TNF-α (Li et al., 2020). In this process, lycopene may regulate DNA methylation-related enzymes, and induce changes in a series of inflammatory factors, thereby improving the behaviors associated with PTSD to a certain extent.

EGCG can also regulate DNA methylation, mostly by inhibiting DNMT. Further to this, it can inhibit the activity of dihydrofolate

Table 5
Preclinical and clinical studies investigating role of DNA methylation in PTSD.

Diseases	Cases	Markers	Main results	Main mechanisms	References
Preclinical studies	Control ($n = 10$) Susceptibility ($n = 7$–16) Resilient ($n = 7$–16)	Western blotting DNMT3a	Susceptibility vs Resilient: ↓DNMT3a protein and mRNA expression in NAc	DNMT	Warhaftig et al., 2021
	Extinction: 5-HTT$^{-/-}$; 5-HTT$^{+/+}$ ($n = 8$) No-extinction: 5-HTT$^{-/-}$; 5-HTT$^{+/+}$ ($n = 8$)	Immunofluorescence 5-mC 5-hmC	Extinction vs No-extinction: ↓5-hmC in BLA and CA in 5-HTT$^{-/-}$ rats ↔5-hmC in BLA and CA in 5-HTT$^{+/+}$ rats ↔5-mC in 5-HTT$^{+/+}$ and 5-HTT$^{-/-}$ rats	DNMT TET	Shan, Guo, van den Heuvel, van Heerikhuize, & Homberg, 2018
	Stress ($n = 10$) No stress ($n = 10$)	BSP BDNF DNA methylation	Stress vs no stress:↓BDNF exon IV DNA methylation in ventral CA3 ↑BDNF exon IV DNA methylation in dorsal DG and dorsal CA1 ↔BDNF exon IV DNA methylation in dorsal CA3, ventral CA1 and DG	DNMT	Roth, Zoladz, Sweatt, & Diamond, 2011
Clinical studies	PTSD ($n = 199$)	SKA2	↑SKA2 DNA methylation with the increasing of PTSD severity	DNMT	Sadeh et al., 2016
	PTSD ($n = 309$)	KL	↑KL DNA methylation with the increasing of PTSD severity	DNMT	Wolf et al., 2020
	Control ($n = 47$)PTSD ($n = 47$)	AIM2	PTSD vs Control: ↓AIM2 methylation ↑AIM2 gene expression	DNMT	Mc et al., 2021
	Control ($n = 23$) PTSD + tf-CBT with EMDR ($n = 23$) PTSD + tf-CBT without EMDR ($n = 11$)	ZFP57	EMDR vs no EMDR ↑ZFP57 methylation	DNMT	Vinkers et al., 2021

Note: [a] ↓ decreased, ↑ increased, ↔ unchanged. [b] Abbreviations: AIM2, absent in melanoma 2; BSP, bisulfite sequencing PCR; EMDR, eye movement desensitization reprocessing; NAc, nucleus accumbens; KL, klotho; SKA2, spindle and kinetochore-associated protein 2; TET, translocation methylcytosine dioxygenases; tf-CBT, trauma-focused cognitive behavioral therapy; ZFP57, zinc-finger protein 57; 5-HTT$^{+/+}$, serotonin transporter no-knockout; 5-HTT$^{-/-}$, serotonin transporter knockout; 5-mC, 5-methylcytosine; 5-hmC, 5-hydroxymethylcytosine.

Fig. 3. Effects of various natural products on DNA methylation in PTSD. DNA methylation occurs under the action of DNA methyltransferase, and DNA methylation has multiple sites of action. Reports related to PTSD have shown that BDNF, TNF, AIM2, SKA2, KL and other gene loci have different levels of DNA methylation. In addition, natural products can regulate methylation levels at different sites by affecting the expression of DNA methyltransferase, which in turn affects the expression of related factors such as BDNF or TNF in PTSD patients.

reductase, and then inhibit DNA synthesis to alter DNA methylation (Navarro-Peran et al., 2005). In conclusion, the epigenetic regulation mechanism of EGCG in the treatment of PTSD is not only limited to histone modifications but also involved DNA methylation and noncoding RNA. In addition, extracted vitamin C has also been used in the treatment of PTSD. Studies have shown that in addition to increasing the activity of KDM, extracted vitamin C can also increase translocation methylcytosine dioxygenases (TET), mediate the demethylation process, promote transcription, catalyze the oxidative removal of methyl groups of histone lysine residues, and maintain the normal progression of development (Coker, Smith-Diaz, Dyson, Vissers, & Berry, 2022). A reduction in oxidative stress in the hippocampus was also shown to prevent memory impairment in PTSD mice. In conclusion, the effects of vitamin C on reducing oxidative stress in PTSD may be related to its effect on epigenetic enzymes, but further verification is required. Vitamin E can also act as an epigenetic regulator to interfere with oxidative stress-induced disease. For example, vitamin E in obesity can regulate the methylation status of the DNA repair gene MLH1 and control its expression by upregulating DNMT1

expression, thereby reducing DNA damage (Remely et al., 2017). In a tumor-related study, BER was also found to inhibit DNMT1 and DNMT3B. For example, curcumin, extracted from turmeric, has a major effect on the aging process, and can significantly improve the process of memory formation in aging animals (Flores, 2017). Furthermore, there is evidence that curcumin has a role in impairing fear memory consolidation and reconsolidation processes in PTSD (Monsey et al., 2015). Curcumin can regulate several different pathways, including DNMT inhibition, HAT, and HDAC activity regulation and miRNA expression regulation, and it also plays a role in gene expression modification (Guo et al., 2018; Momtazi et al., 2016; Montagud-Romero et al., 2016; Yan et al., 2017). Furthermore, curcumin has anti-inflammatory effects and can reduce the expression of several genes regulated by NF-κB, such as interleukin and TNF. Hence, it is possible that curcumin treatments for PTSD may work through one or more of these pathways, which need to be further elucidated. Other natural products capable of regulating the onset or progression of disease by regulating DNA methylation levels are summarized in Table 6. Similar with the histone modifications, the mechanisms of DNA methylation in response to natural products in PTSD remains unclear.

2.3. Noncoding RNA

Noncoding RNAs (ncRNAs) are the products of DNA transcription, and ncRNAs are different from other RNAs as they are not translated into proteins to participate in physiological processes. However, ncRNAs, are functional RNAs, as they are involved in processes such as RNA processing and regulation (Howie, Rijal, & Ressler, 2019; Schmidt, Keck, & Buell, 2015). There are a huge number of ncRNA genes, including RNAs with relatively small molecular weights, such as microRNAs (miRNAs), piwi-interaction RNAs (pi RNAs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), and long noncoding RNAs (lncRNAs) with relatively large molecular weights and retrotransposons (Daskalakis, Provost, Hunter, & Guffanti, 2018; Eddy, 1999; Howie, Rijal, & Ressler, 2019). miRNAs usually work by inhibiting the expression of post-transcriptional genes (Mendell & Olson, 2012). In addition, long noncoding RNAs mainly bind to chromatin modification proteins and are involved in altering chromatin states and influencing subsequent gene expression. This type of RNA is often an ideal drug target as it can be used to achieve time and space specificity (Sandberg, Samson, & Ji, 2013). Previous studies of noncoding RNAs in psychiatric diseases have focused more on miRNAs, lncRNAs, and retrotransposons in relation to PTSD and these are often used as biomarkers.

Approximately 70 % of miRNAs are expressed in the human nervous system (Cao, Yeo, Muotri, Kuwabara, & Gage, 2006), and they can regulate RNA stability and RNA translation, mainly by inhibiting gene expression (Daskalakis, Provost, Hunter, & Guffanti, 2018). It is thus possible that miRNAs may affect the development of multiple brain regions. In addition, there is increasing evidence that abnormal miRNA expression may lead to a series of neurological diseases, and they may also play a critical role in neurodevelopment or other functions. For example, the dysregulation of miRNAs in *BDNF* and *FKBP5* genes can affect PTSD susceptibility and resilience (Maurel et al., 2021).

According to clinical and animal studies, multiple systems, such as PTSD patients are affected to some extent in patient systems. The effect of miRNAs on the immune system has been implicated in the development of PTSD. For instance, the downregulation of miRNAs may cause changes in the expression levels of related inflammatory factors. A preclinical experiment that dissected the relationship between the level of miR-142 and inflammatory factors found that inhibiting the expression of miR-142 could reduce the level of inflammatory cytokines such as IL-6, IL-1β, and TNF-α. They also suggested that lower miR-142 levels could improve PTSD-like symptoms in rats (Nie et al., 2021). Another study found that the levels of epigenetic regulation in certain genes such as TP53 affect susceptibility to inflammation in patients with PTSD (Busbee et al., 2021). There is thus a need to understand the epigenetic mechanisms of PTSD from the perspective of inflammation. Furthermore, miRNAs play a critical role in the regulation of PTSD. In addition to the aforementioned effects of miR-142 on inflammation, miR-132 may also modulate PTSD symptoms by affecting vulnerable X-family RNA-binding proteins (Nie et al., 2021). In a clinical experimental study, the expression of an enzyme that regulates miRNA production was found to affect the function of AMY, as reduced DICER1 can increase the activation of AMY to fearful stimuli (Wingo et al., 2015). Currently, the use of miRNAs as therapeutic targets to alleviate fear or other symptoms holds great promise. In a previous animal experiment, the administration of fluoxetine to mice was found to relieve PTSD symptoms. At the same time, the experimental results indicated that the reduction of PTSD-like symptoms was associated with the reduction of miRNA levels (Schmidt et al., 2013). Therefore, a better understanding of the underlying mechanisms by which miRNAs function in the body will aid in the development of more effective and promising drugs for PTSD. Additional studies on miRNAs in animals and humans are presented in Table 7. As mentioned, in addition to miRNAs in the noncoding RNAs involved in the development of PTSD, lncRNAs also play a role in this process. LncRNAs can modulate splicing and affect the stability of messenger RNA (mRNA), are highly abundant in the brain, and are closely related to neurodevelopment. An animal study found that lncRNAs affected fear extinction function in patients (Malan-Muller et al., 2020). Further

Table 6
Common natural products that can regulate DNA methylation.

Chemicals	Epigenetic regulation	References
CUR	↑TNF DNA methylation ↓DNMT	Guo et al., 2018; Yan et al., 2017
HSD	↓DNA methylation	Fernandez-Bedmar et al., 2017
Lycopene	↑DNA demethylation	King-Batoon, Leszczynska, & Klein, 2008
Silibinin	↓DNMT	Anestopoulos et al., 2016
GEN	↓DNMT	Li, Liu, Andrews, & Tollefsbol, 2009
Vitamin E	↑DNMT1 and DNMT3B ↓DNMT3A	Coupland et al., 2014
BER	↓DNMT1 and DNMT3B	Liu, Meng, Wu, Qiu, & Luo, 2019
Vitamin C	↑TET	Coker, Smith-Diaz, Dyson, Vissers, & Berry, 2022
CB	↑Rgs7 DNA methylation	Tomas-Roig et al., 2017
Cot	↑AGER DNA methylation	Fuemmeler et al., 2021

Note: [a] ↓ decreased, ↑ increased. [b] Abbreviations: BER, berberine; CB, cannabinoids; Cot, cotinine; CUR, curcumin; DNMT, DNA methyltransferase; GEN, genistein; HSD, hesperidin; TET, Ten-eleven translocation.

Table 7
Preclinical and clinical studies investigating the role of noncoding RNA in PTSD.

Diseases	Cases	Markers	Main results	Main mechanisms	References
Preclinical studies	Control (*n* = 12) Susceptible (*n* = 7)Resilient (*n* = 11)	RT-qPCR miR-15a-5p miR-497a-5p miR-511-5p	Susceptible *vs* Resilient: ↓miR-511-5p, miR-15a-5p and miR-497a-5p expression in HIP and hypothalamus	miRNA	Maurel et al., 2021
	Control (*n* = 24)PTSD (*n* = 24) Sh-miR-NC (*n* = 12)Sh-miR (*n* = 12)	RT-qPCR miR-132	PTSD *vs* Control: ↑miR-132 in HIP	miRNA	Nie et al., 2021
	Control (*n* = 12)PTSD (*n* = 12) Sh-miR-NC (*n* = 12) Sh-miR-antisense (*n* = 12)	RT-qPCR miR-142	PTSD *vs* Control: ↑miR-142 in HIP Sh-miR-antisense *vs* Sh-miR-NC: ↓miR-142 and PTSD-like behavior	miRNA	Nie et al., 2021
	Vehicle-no shock (*n* = 6) Vehicle-shock (*n* = 6)Fluoxetine-no shock (*n* = 6) Fluoxetine-shock (*n* = 6)	RT-qPCR miR-1971 miR-1947-3p miR-33-5p	Fluoxetine treatment *vs* shock: ↓miR-1971 in mPFC ↓miR-1947-3p in mPFC ↑miR-33-5p in mPFC	miRNA	Schmidt et al., 2013
	Control (*n* = 10)PTSD (*n* = 10)	RT-qPCR lncRNA	PTSD *vs* Control:↑143 lncRNAs in hippocampus ↓150 lncRNAs in hippocampus	lncRNA	Qingzhen et al., 2016
Clinical studies	Control (*n* = 24)PTSD (*n* = 24)	RT-PCR Has-miR-7113-5p	PTSD *vs* Control: ↓ Has-miR-7113-5p	miRNA	Bam et al., 2020
	Control (*n* = 17)PTSD (*n* = 16)	qRT-PCR Has-miR-193a-5p	PTSD *vs* Control: ↓ Has-miR-193a-5p	miRNA	Bam et al., 2016
	Control (*n* = 4)PTSD (*n* = 8)	qRT-PCR miRNA let-7a miR-145 miR-16 miR-221 miR-320b	PTSD *vs* Control: ↓miRNA let-7a, miR-145, miR-16, miR-221, miR-320b	miRNA	Busbee et al., 2021
	Control (*n* = 5)PTSD (*n* = 5)	qRT-PCR miRNA	PTSD *vs* control: ↓most of the miRNA in PMBC	miRNA	Bam et al., 2017
	Control (*n* = 72) PTSD + depression (*n* = 112)	RT-PCR miRNA	PTSD *vs* Control: ↓miRNA	miRNA	Wingo et al., 2015

Note: [a] ↓ decreased, ↑ increased. [b] Abbreviations: lncRNA, long noncoding RNA; miR, microRNA; HIP, hippocampus; PMBC, peripheral blood mononuclear cell; qRT-PCR, quantitative real-time PCR; RT-qPCR, reverse transcription quantitative real-time PCR.

animal studies also showed that multiple lncRNAs were differentially expressed between PTSD and control rats (Qing et al., 2016). However, overall, research on lncRNAs associated with PTSD is lacking.

A review of numerous studies found that miRNA regulation by natural products is relatively common in cancer treatments. For example, natural products can be used to treat various diseases such as leukemia, liver cancer, pancreatic cancer, and cervical cancer (Chen et al., 2020; Liao, Lin, Chen, Lin, & Au, 2014; Ma et al., 2021), as well as PTSD. In addition to the anti-inflammation and anti-oxidation stress effects mentioned, some products also have certain regulatory effects on apoptosis and autophagy. This can adjust miRNA expression levels to regulate apoptosis and autophagy-related factors *in vivo*, thereby affecting the development of disorders (Park et al., 2017). GAS, catapol, puerarin, hesperidin (HSD), crocin (CROC), and glycyrrhizin (GLC) reportedly have miRNA regulatory effects, and have been shown to inhibit the expression of inflammatory factors and the occurrence of inflammation.

Multiple studies have indicated that GAS can alter the content of various noncoding RNAs, including long noncoding RNAs and miRNAs, and the main mechanism of action is that lncRNA binds to endogenous miRNA, which, as a noncoding RNA, mainly inhibits

the expression of target mRNA (Li, Wang, Yan, & Zhang, 2022; Shu et al., 2021). Like GAS, it also has anti-inflammatory, anti-oxidative stress, and anti-apoptotic effects. GAS increases beclin-1, Bax, and light chain 3 (LC3) and reduces bcl-1 and p6 in specific brain regions through its anti-apoptotic effects. Meanwhile, GAS can also regulate miRNA497 and play a role in regulating neuronal death and survival through autophagy (Li, Wang, Yan, & Zhang, 2022). In addition, GAS can also regulate lncRNA NEAT1 and miRNA-22-3p to reduce inflammation and brain injury (Zhang, Ouyang, Ji, & Liu, 2021). In conclusion, GAS has a certain neuroprotective role and can effectively treat memory disorders and fear disorders after trauma. Some studies have indicated that GAS can improve the learning and spatial memory ability of PTSD patients to a certain extent (Lei, Yuan, & Zou, 2020). Therefore, the regulation of noncoding RNAs by natural products may be involved in the regulation of PTSD through apoptosis or autophagy. Catapol has been implicated to alleviate PTSD symptoms, mainly by inhibiting the expression of lncRNA Neat1, which reduces miR-140-5p transcription and upregulates HDAC4 expression (Zou et al., 2019). In addition, puerarin, HSD, and CROC can upregulate the levels of miR-140-5p, miR-132, and miR-122, respectively, to inhibit the expression of proinflammatory related factors and exert anti-inflammatory effects (Li, Shao, Zhang, & Qin, 2016; Liu et al., 2019; Xu, Xiong, Xu, & Xu,

2020). In addition, GLC functions mainly by reducing the expression of miR-222 (Ito, Loucas, Suzuki, Kobayashi, & Suzuki, 2020). Although the specific mechanisms of PTSD treatment are unclear, we have speculated that these natural products may affect the expression of genes related to PTSD symptoms through the regulation of miRNA, which needs to be further studied. The roles of basic noncoding RNAs and common natural products that regulate noncoding RNAs are summarized in Fig. 4. In addition, the epigenetic regulatory utility of natural products used to treat PTSD has been summarized in Table 8 (Fig. 5).

3. Toxicology and side effects

Reports of the toxic side effects that occur when using natural products as therapeutics for PTSD are rare. When chemical drugs are used to treat diseases, the onset of their effects is fast and perhaps also significantly curative, but they also have unavoidable toxic side effects on the human body. Consequently, the use of medicinal plants and some natural products has gradually been increasing in popularity due to their perceived safety. At present, although chemical drugs occupy a larger pharmaceutical market, with the increase in human health needs, natural products have also received increasing attention owing to their low toxicity and low levels of side effects. In addition, natural products have been shown to be effective against various diseases, including PTSD. Currently, natural products are predominantly used on a large scale for the treatment of cancer and tumors, for which chemotherapy and Western medicine are indispensable, but these often result in significant side effects or even irreversible damage to the human body. The excellent characteristics of plant extracts are often used to alleviate or prevent the occurrence of side effects. Although natural products are generally characterized as having fewer side effects and lower toxicity levels, they cannot be considered completely harmless to the human body. For example, berberine may cause insufficient glucose-6-phosphate dehydrogenase levels in pregnant women and neonates, leading to hemolysis. In addition, the combination of berberine and other Western medicines may produce a series of gastrointestinal reactions (Pang et al., 2015). Moreover, some extracts are developmentally toxic and neurotoxic, such as cannabinoids (Huestis et al., 2019). The side effects of these natural products are often dose-related, and only when taken within a safe dose range will achieve their expected efficacy. For example, resveratrol has been shown to be a safe compound when in the human body, but there are also reports in the literature that it may have negative side effects, such as cytotoxicity (Shaito et al., 2020). Therefore, the use of natural products or medicinal plants requires that people understand dosage so that they know how to best avoid any toxic side effects.

4. Discussion and conclusion

Sudden violent incidents and natural disasters are increasing globally (Raman et al., 2021), and consequently, so are mental illnesses such as PTSD. PTSD is a very complex psychiatric disorder, and while its pathogenesis is still unclear, there is sufficient evidence that epigenetics can regulate its occurrence. Here, we have focused on the role of epigenetic regulations in PTSD and the mechanisms by which common natural products are involved in these processes and can thus be utilized in treatment strategies.

Since ancient times, the natural environment has been a rich source of medical resources, as evidenced by the documentation of Chinese herbs and plants that have medicinal effects. The biolog-
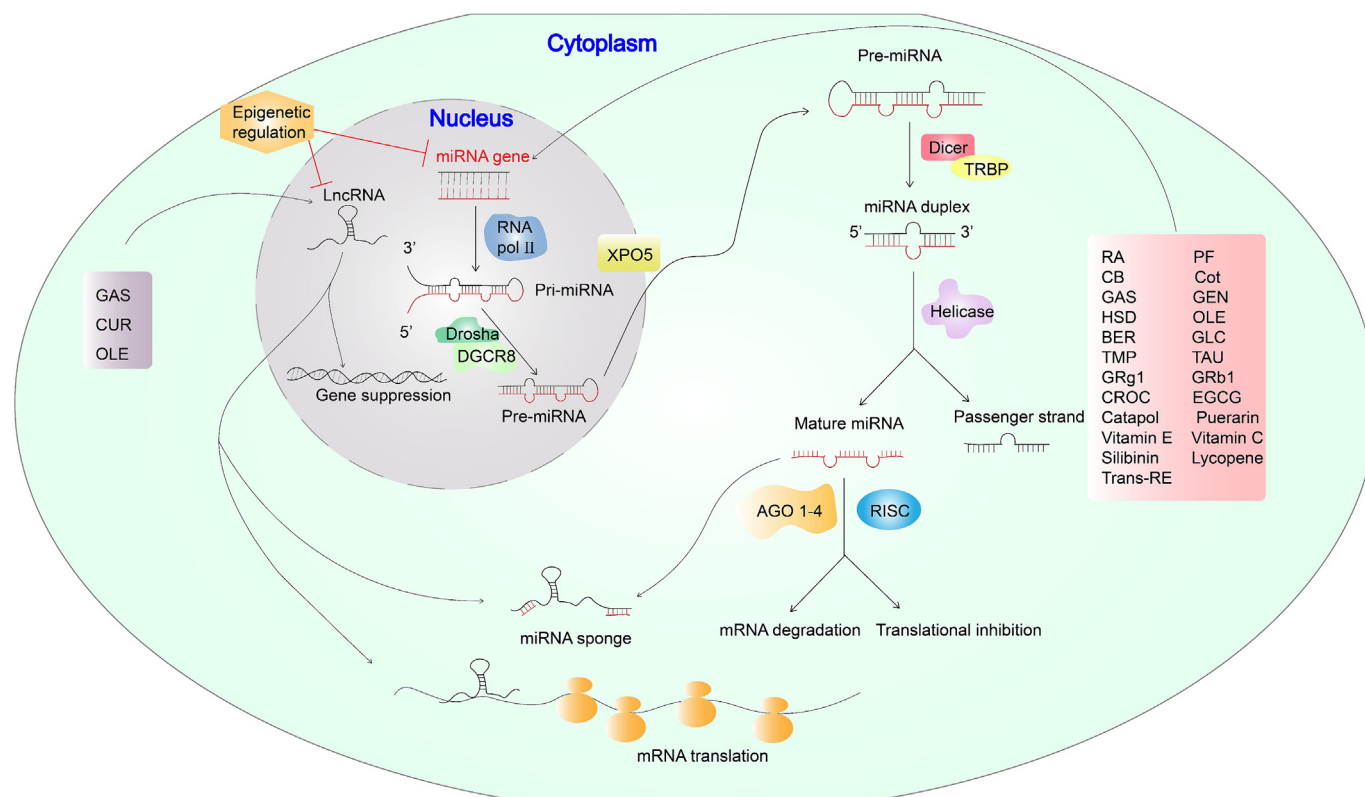
Fig. 4. Various natural products and their effects on noncoding RNA in PTSD. The regulation of non-coding RNA mainly includes the regulation of miRNA and LncRNA. Both affect transcriptional activation and inhibition in different ways of action. A large number of natural products, including RA, GAS, GRg1, GRb1, EGCG, can regulate and change the levels of different types of miRNAs through epigenetic regulation, so as to achieve the purpose of transcriptional activation or inhibition, and then regulate the level of miRNA in PTSD patients. Natural products such as GAS, CUR and OLE can also exert therapeutic effects by regulating LncRNA.

Table 8
Common natural products that can regulate noncoding RNA.

Chemicals	Epigenetic regulation	References
RA	↓miR-642a-3p and miR-6785-5p	Yu et al., 2019
Catalpol	↓miR-140-5p	Xiong et al., 2017
	↓miR-132	
GAS	↑miR-22-3p	Li, Xiao, & Chen, 2022; Shu et al., 2021; Zhang, Ouyang, Ji, & Liu, 2021
	↓miR-142a	
	↓miR-497	
	↑lncRNA Gm7237	
	↓↓lncRNA NEAT1	
GRg1	↓miR-21	Kwok et al., 2017; Zhai et al., 2021
	↓miR-15b, miR-23a and miR-214	
GRb1	↓miR-134	Wang et al., 2022; Wilkes et al., 2021
	↑miR-208	
PF	↓miR-15b	Huang, Li, Chen, Fan, & Yu, 2021; Wang et al., 2021
	↑miR-124	
trans-RE	↓miR-132 and miR-15a	Eseberri, Lasa, Miranda, Gracia, & Portillo, 2017; Isac et al., 2017
	↑miR-155, miR-134 and miR-124	
CUR	↓oncomiRs	Momtazi et al., 2016
Puerarin	↓miR-140-5p	Xu et al., 2020
	↓miR-21	
HSD	↑miR-132	Li et al., 2016; Magura, Hassan, Moodley, & Mackraj, 2021
	↓miR-155 and miR-21 in MCF-7	
EGCG	↑miR-16	Tsang & Kwok, 2010
Silibinin	↓miR-155	Dupuis et al., 2018
GEN	↑miR-451	Gan et al., 2019
OLE	↑miR-137, miR-181b and Let-7d	Tezcan et al., 2019
GLC	↓miR-222	Ito, Loucas, Suzuki, Kobayashi, & Suzuki, 2020
	↑LncRNA-Gas5	
Vitamin E	↓miR-126, miR146a and miR-124	Ambrogini et al., 2018
TMP	↑miR-182	Li et al., 2019
BER	↓miR-152, miR-29a and miR429	Liu et al., 2019
Lycopene	↑miR-21	Ahn, Lee, Jung, & Ha, 2012
TAU	↑miR-122-5p	Nabi, Atta, El-Ahwany, Elzayat, & Saleh, 2021
CB	↑miR-29b1	Scherma et al., 2020
Cot	↑miR-223	Herberth et al., 2014
CROC	↑miR-9 and miR-29	Khedr, Rahmo, Farag, Schaalan, & El Magdoub, 2020; Vahdati Hassani, Mehri, Abnous, Birner-Gruenberger, & Hosseinzadeh, 2017
	↓miR-122	

Note: [a] ↓ decreased, ↑ increased. [b] Abbreviations: BER, berberine; CB, cannabinoids; CROC, crocin; Cot, cotinine; CUR, curcumin; EGCG, epigallocatechin gallate; GAS, gastrodin; GEN, genistein; GLC, glycyrrhizin; GRb1, ginsenoside Rb1; GRg1, ginsenoside Rg1; HSD, hesperidin; OLE, oleuropein; PF, paeoniflorin; RA, rosmarinic acid; TAU, taurine; TMP, tetramethylpyrazine.

ically active natural products in some medicinal plants can thus be used to help develop new drugs. Consequently, screening desirable natural products from traditional Chinese medicines and medicinal plants is an ongoing process. With the development and progress of science and technology, researchers have found that simply screening new drugs through traditional drug discovery and design methods is very unrealistic, as the process is time-consuming, human and material resources can easily be wasted, and the effects may not be significant. However, in recent years, computer technologies in the field of virtual screening and drug design have rapidly developed with continuous innovation, and the results have been remarkable (Lin, Zhang, Wang, Yang, & Shen, 2022). In addition, affinity-based screening has also notably added in the identification of active ingredients from complex ingredients and further promoted drug discovery. For example, affinity chromatography, biological chromatography, affinity electrophoresis, magnetic screening, fluorescence polarization, surface ionization resonance, and other methods are now more accurate and effective for use with drug discovery; however there are also certain shortcomings (Hou et al., 2020). The screening of natural products requires more researchers to carry out careful step-by-step investigations, and develop a more comprehensive and efficient screening method. Moreover, natural products have proven to be effective at treating and ameliorating different diseases, and while most research has been conducted on cancer, there is also evidence that natural extracts can improve PTSD symptoms. When com-

pared with chemical treatments, natural product treatments are widely perceived as being safer. PTSD is complicated by many influencing factors, such as the traumatic event itself, the external environment of the patient, and their familial genetic history. However, the pathophysiological basis of PTSD is also complex, and multiple systems in the body are related to the occurrence of disease. The results of this literature review show that epigenetic regulation is mainly divided into three parts: histone modification, DNA methylation, and noncoding RNA, while changes in the histone, DNA, and noncoding RNA also affect the occurrence of PTSD to a certain extent. Although there are few reports on the side effects of the natural products that can be used to treat PTSD due to their low toxicity, it has been reported in the literature that natural products can have toxic side effects in the treatment of other diseases, so its disadvantages cannot be ignored. In addition, although the number of articles on the role of natural products in PTSD from the perspective of epigenetic regulation is limited or even scarce, the number of articles related to the epigenetic regulation of natural products in the treatment of other diseases is sufficient. The use of natural products to treat PTSD is gradually being adopted, and there is a plethora of available literature and reviews on how to understand PTSD from the perspective of epigenetic regulation. Consequently, studying the effects of natural products on PTSD is a promising field of research. In summary, although there are unresolved problems regarding the use of natural products, in view of their advantages such as low toxicity, few
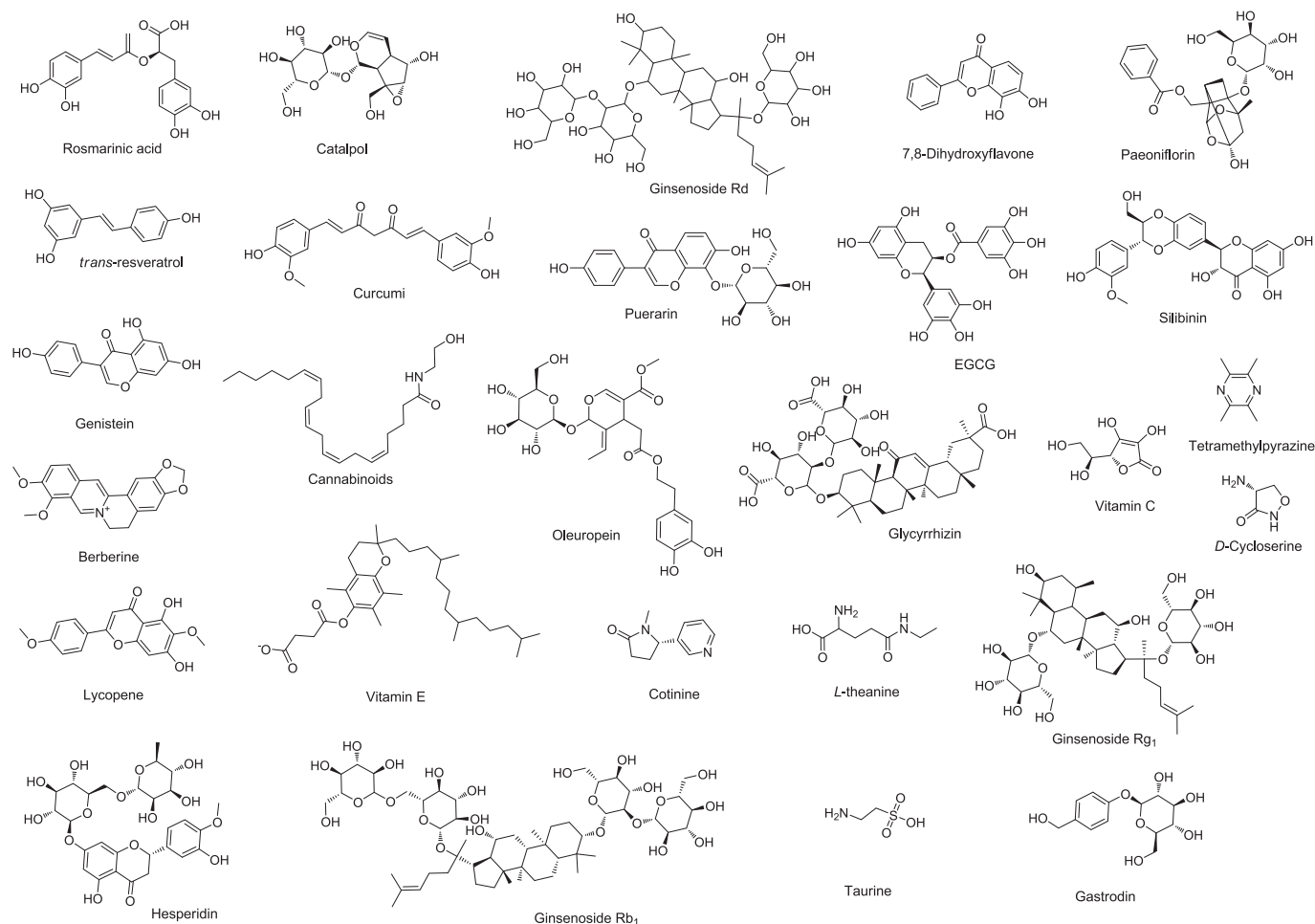
Fig. 5. Chemical sructures of various natural products on histone acetylation and methylation in PTSD.

adverse reactions, and ability to regulate epigenetics in numerous ways, they have great developmental potential for the field of psychiatric disease treatment, such as for PTSD.

CRediT authorship contribution statement

Meijing Xu: Conceptualization, Investigation, Visualization, Writing – original draft. **Minghui Cui:** Investigation, Writing – review & editing. **Yu Wang:** Conceptualization, Investigation, Visualization, Writing – original draft. **Boru Li:** Investigation, Methodology. **Lijin Feng:** Investigation, Methodology. **Hang Xing:** Supervision, Writing – review & editing. **Kuo Zhang:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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