



## Research progress in the regulation of secondary metabolism in medicinal plants by MYB transcription factors



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### ABSTRACT

MYB transcription factors (MYB TFs) are one of the largest families of transcription factors in plants, which are widely involved in various fields of plant growth and development, and play an important regulatory role in the biosynthesis of plant secondary metabolites. Most of the current studies on MYB transcription factors have focused on agricultural crops, and fewer studies have been conducted on medicinal plants. Therefore, this study reviews the research progress of plant MYB transcription factors in secondary metabolism of medicinal plants, which provides ideas and methods for better utilisation and development of medicinal plants.

### 1. Introduction

Transcription factors, also known as *trans*-acting factors, usually refer to a multifunctional protein encoded by genes that specifically bind to relevant *cis*-acting elements in the promoter regions of downstream target genes to activate their expression.<sup>1</sup> The MYB family of transcription factors is one of the largest families of transcription factors in plants, with a wide range of biological functions such as involvement in plant growth and development, metabolism of physiological activities, cellular morphology and pattern building, primary and secondary metabolic responses, response to biotic or abiotic stresses.<sup>2,3,4,5,6</sup> In recent years, there have been many studies related to plant MYB transcription factors from different aspects, revealing that MYB plays different roles in different developmental stages of plants. However, there are few specific studies on medicinal plants, and even fewer studies on the role of MYB transcription factors in the regulation of secondary metabolism in medicinal plants. The secondary metabolites of medicinal plants are affected by many factors,<sup>7</sup> and MYB transcription factors play a great role in the secondary metabolism of medicinal plants, which deserves further investigation. Therefore, this study reviews the role of MYB transcription factors in the secondary metabolism process of medicinal plants based on the previous research results, which may be an important reference value for some people who aim to cultivate or modify medicinal plants capable of yielding higher content of medicinal components.

### 2. Structure and classification of MYB transcription factors

Common feature of MYB TFs is the conserved DNA-binding domain (MYB structural domain), which interacts with DNA. In general, the MYB structural domain usually consists of 1–4 incomplete repeats in plants. Each repeat encodes three  $\alpha$ -helices containing approximately 50–53 amino acids.<sup>8–10</sup> Of these three helices, the second and third helices form a helix-turn-helix (HTH) structure.<sup>11</sup> MYB transcription factors can be inserted into the major groove of target DNA through the HTH structure and then bind to target DNA to regulate the expression of target genes.<sup>12</sup> Generally, each MYB repeat structural domain contains three conserved tryptophan residues that are separated by 18–19 amino acids to form a secondary structure. Based on the number of MYB structural domains, MYB TFs in medicinal plants can be classified into four subfamilies (Fig. 1): the 1R-MYB family, the R2R3-MYB family, the 3R-MYB family and the 4R-MYB family. 1R-MYB, which contains a single MYB structural domain, plays an important role in the regulation of plant transcription and the maintenance of chromosome structure.<sup>13</sup> 2R-MYB contains two MYB structural domains and is the most widely present protein in medicinal plants, regulating transcription of secondary metabolic processes and regulating cell differentiation. 3R-MYB subfamily members contain three MYB structural domains and are largely associated with the regulation of cell differentiation and involvement in cell cycle control.<sup>14</sup> In medicinal plants, the 4R-MYB subfamily is also the smallest class in the

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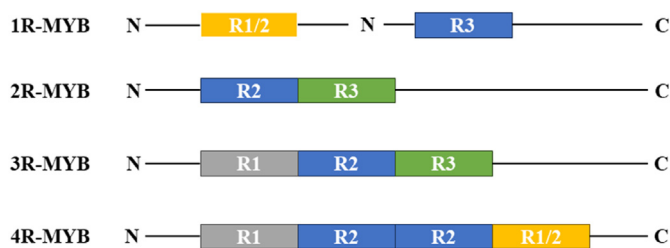


Fig. 1. Classification of plant transcription factors MYBs.

MYB family, and the functions of the 4R-MYB subfamily members need to be further investigated.

### 3. Current status of research on the regulation of secondary metabolism in medicinal plants by MYB transcription factors

#### 3.1. Role in the biosynthesis of flavonoids

Flavonoids are important secondary metabolites in medicinal plants, with anthocyanins, flavonols and isoflavones being important components.<sup>15</sup> As a class of multifunctional compounds, including regulation of plant growth, resistance to UV-B damage, cell wall formation and defence against diseases,<sup>16</sup> they also possess a wide range of pharmacological activities such as antioxidant,<sup>17</sup> anti-inflammatory,<sup>18</sup> antimicrobial,<sup>19</sup> anticancer<sup>20</sup> and inhibition of cardiovascular diseases.<sup>21</sup>

The biosynthetic pathways of flavonoids are shown in Fig. 2. In addition to regulating key functional genes, flavonoid biosynthesis is also regulated by MYB TFs.<sup>22,23</sup> It was shown that most of the MYB transcription factors act as positive regulators to regulate flavonoid biosynthesis. The transcription factors GtMYBP4 and GtMYBP3 from *Gentiana triflora* Pall both activate the expression of flavonol biosynthesis genes (*CHS*, *ANR*, *LAR*, and *ANS*), and when heterologously expressed in *Gentiana triflora* Pall, they can increase the flavonol content;<sup>24</sup> the MYB transcription factors controlling anthocyanin or flavonol biosynthesis pathways were identified: EsMYBA1, EsAN2 and EsMYBF1, and their functions were characterised,<sup>25–28</sup> and EsMYBF1 was found to strongly activate the promoters of the *EsF3H* and *EsFLS* genes, which are related to

flavonol biosynthesis in *Epimediium brevicornu* Maxim;<sup>29</sup> FtMYB15, a MYB similar to SG4, plays an active role in Arabidopsis anthocyanin/PA biosynthesis in *Fagopyrum tataricum* (L.) Gaertn;<sup>30</sup> the MYB transcription factor MtPAR regulates proanthocyanidin biosynthesis in *Medicago sativa* L.<sup>31</sup>

Meanwhile, a small number of MYB transcription factors are also involved in the synthesis of flavonoids as negative regulators. Li<sup>32</sup> et al. demonstrated that the *Camellia sinensis* (L.) O. Ktze CsMYB4a repressed the promoter activity of five phenylpropanoid pathway genes (*CsANR*, *CsLAR*, *CsCHS*, *Cs4CL*, and *CsC4H*) and inhibited the synthesis of phenylalanine and flavonoids; the FtMYB8 inhibited anthocyanin/PA accumulation by strongly down-regulating the *AtTT12* gene in *Fagopyrum tataricum* (L.) Gaertn;<sup>33</sup> Xu<sup>34</sup> et al. found that the transcript levels of the genes *CHS*, *F3H*, *FLS*, and *ANS* were significantly reduced, and the synthesis of flavonoids and anthocyanins was inhibited when the *Ginkgo biloba* L transcription factor GbMYBF2 was overexpressed in Arabidopsis.

The biological process of flavonoid synthesis in medicinal plants is cross-regulated by multiple branching pathways, and MYB transcription factors can differentially regulate the expression of various genes in time and space. Overexpressing the *Epimediium brevicornu Maxim* transcription factor EsMYBF1 in tobacco, the structural genes involved in flavonol synthesis, *NtCHS*, *NtCHI*, *NtF3H*, and *NtFLS*, were significantly up-regulated, whereas the genes for late biosynthesis in the anthocyanin pathway (*NtDFR* and *NtANS*) were significantly down-regulated.<sup>25</sup> Meanwhile, MYB transcription factors can also interact with other transcription factors to regulate flavonoid synthesis; EsMYBA1 interacts with several bHLH regulators of the flavonoid pathway and activates the promoters of *DFR* and *ANS* to regulate flavonoid biosynthesis in *Epimediium brevicornu Maxim*;<sup>26</sup> and EsMYB9 can interact with EsTT8 to induce *NtCHI*, *NtF3H*, *NtF3H*, *NtDFR* and *NtANS* expression of anthocyanin biosynthesis genes.<sup>27</sup>

#### 3.2. Role in terpene biosynthesis

Medicinal plants with a predominance of terpenoids include *Taxus* spp, *Artemisia annua* L, *Panax ginseng* C. A. Mey and *Radix Bupleuri*. Terpenoids include monoterpenes, diterpenes, sesquiterpenes, triterpenes and their derivatives. These terpenoids play important roles in plant growth, development, general metabolism and defence.<sup>35</sup> And they

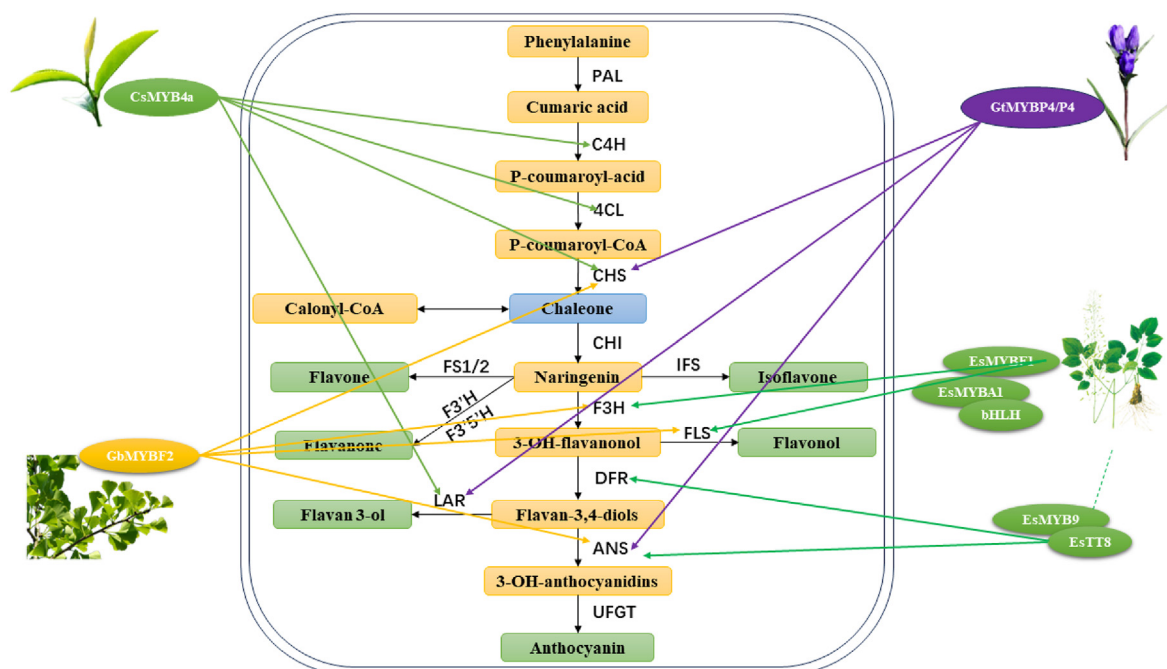


Fig. 2. Flavonoid synthesis pathway and gene regulation in medicinal plants.

have important pharmacological activities such as antibacterial,<sup>36</sup> antioxidant,<sup>37</sup> anticancer<sup>38</sup> and anxiolytic.<sup>39</sup>

Terpenoid biosynthesis occurs through two pathways: the MVA pathway and the MEP pathway (Fig. 3, Fig. 4).<sup>40</sup> It was found that MYB transcription factors regulate terpenoid synthesis mainly by directly regulating the transcriptional expression of structural genes in the terpenoid synthesis pathway and thus regulating terpenoid synthesis. For example, the transcription factor SmMYB9b in *Salvia miltiorrhiza* Bunge up-regulated the expression levels of genes encoding enzymes of the terpene synthesis pathway, such as *SmDXS2*, *SmDXR*, *SmGGPPS*, and *SmK-SL1*, and facilitated the synthesis of tanshinones in *Salvia miltiorrhiza* Bunge by modulating the MEP biosynthetic pathway;<sup>41</sup> the transcription factor TmMYB3 was found to bind directly to the yarrowane 2 $\alpha$ -O-benzoyltransferase gene (*TmTBT*) and the MYB recognition element of the promoter of the paclitaxel 2 $\alpha$ -O-benzoyltransferase gene (*TmTS*) and activate their expression to promote paclitaxel synthesis in *Taxus  $\times$  media* Rehder.<sup>42</sup>

In addition, the MYB transcription factor can also negatively regulate the expression of terpene synthesis pathway enzyme genes and affect terpene biosynthesis. It was found that the *Mentha spicata* L transcription factor MsMYB can inhibit the expression of the geranylgeranyl diphosphate synthase gene *GGPPS*, thereby reducing the accumulation of its catalytic product GPP *in vivo*, and blocking the biosynthesis of monoterpenes, such as limonene and psoralen in *M.*;<sup>43</sup> the *Citrus reticulata* Blanco CrMYB68 directly binds to and significantly inhibits the expression of the carotenoid biosynthetic pathway enzyme genes *CrBCH2* and *CrNCED5* promoters and significantly inhibits their expression; thus inhibiting carotenoid synthesis.<sup>44</sup>

MYB can not only play a regulatory role alone, but also form protein complexes with other transcription factors to participate in the regulation of terpene synthesis. FhMYC2 of *Freesia hybrida* Klatt interacts with FhMYB21L2 to form a protein complex, it interferes with the binding of *FhMYB21L2* to the *FhTPS1* promoter, represses the expression of the *FhTPS1* gene, and then inhibits the synthesis of linalool;<sup>45</sup> TmMYB39 of Mandeville redwoods interacts with TmbHLH13 to form the TmMYB39-TmbHLH13 complex and significantly activated the expression of paclitaxel biosynthesis genes *GGPPS* and *T46OH*, promoting paclitaxel synthesis in *Taxus  $\times$  media* Rehder.<sup>46</sup>

MYB transcription factors can form a cascade of transcriptional regulation with other transcription factors in addition to synergistically regulating terpene synthesis by forming complexes with other proteins. For example, HD-ZIP family proteins AaHD1 and AaHD8 directly activate the expression of MYB transcription factor AaTAR2, which can activate the expression of artemisinin biosynthesis pathway enzyme genes *ADS*, *CYP71AV1*, *DBR2*, and *ALDH1*, and ultimately AaTAR2 and HD-ZIP synergistically promote artemisinin biosynthesis in *Artemisia annua* L.<sup>47</sup>

### 3.3. Role in the synthesis of other substance

MYB transcription factors not only regulate the synthesis of flavonoids and terpenoids, but also the biosynthesis of other secondary metabolites. For example, heterologous expression of the *Chrysanthemum morifolium* Ramat transcription factor CmMYB8 in *Arabidopsis thaliana* down-regulates some genes encoding lignin syntheses, thus inhibiting its biosynthesis;<sup>48</sup> highly expressed *SmMYB39*, the contents of 4-coumaric acid, rosmarinic acid, salvianolic acid, salvianolic acid B, salvianolic acid A, and total phenolics were significantly decreased by down-regulation of the expression of *C4H* and *TAT* in *Salvia miltiorrhiza* Bunge.<sup>49</sup>

## 4. Role of MYB transcription factors in the regulation of medicinal plants in response to abiotic stress and phytohormone responses

Plant growth and development processes cannot be separated from the support of these natural factors such as light, air, water, temperature and soil minerals, etc. However, the bias conferred by these factors will in turn constrain the plant's own growth and development, the plant is subjected to abiotic stresses and grows in adversity. Many MYB transcription factors of medicinal plants have been explored and studied in depth and found to play important roles in the regulation of growth in adversity.

### 4.1. MYB TFs response to drought stress

MYB, as one of the most important transcription factor families in

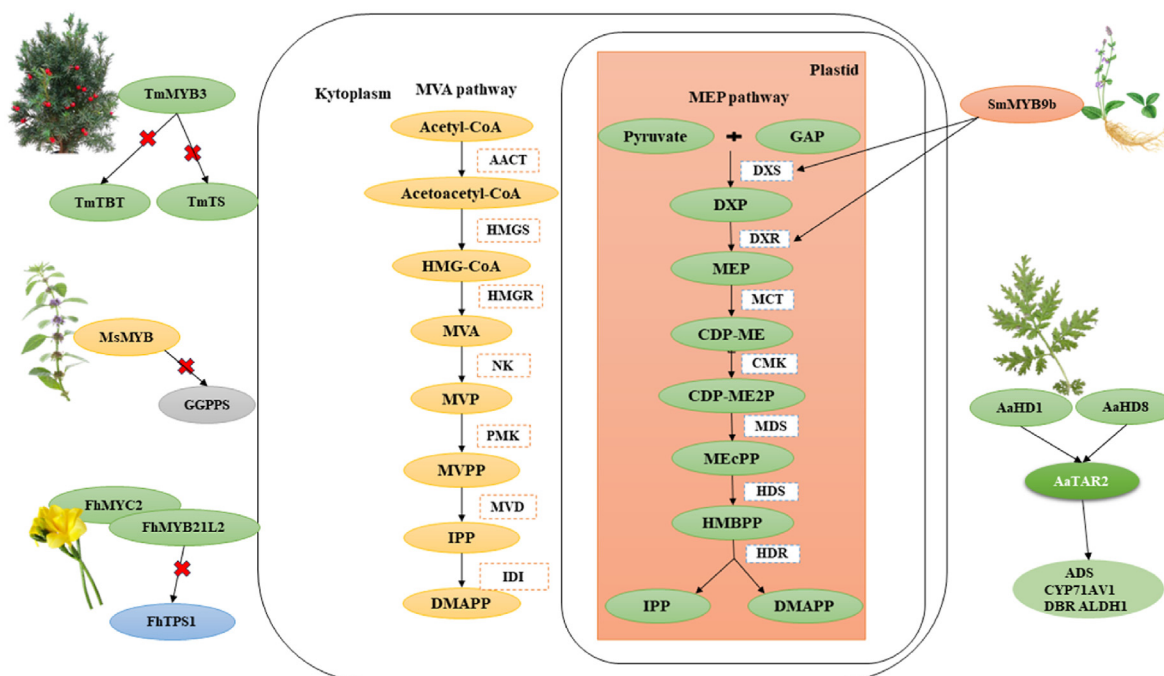


Fig. 3. Terpenoid synthesis pathways and gene regulation in medicinal plant.

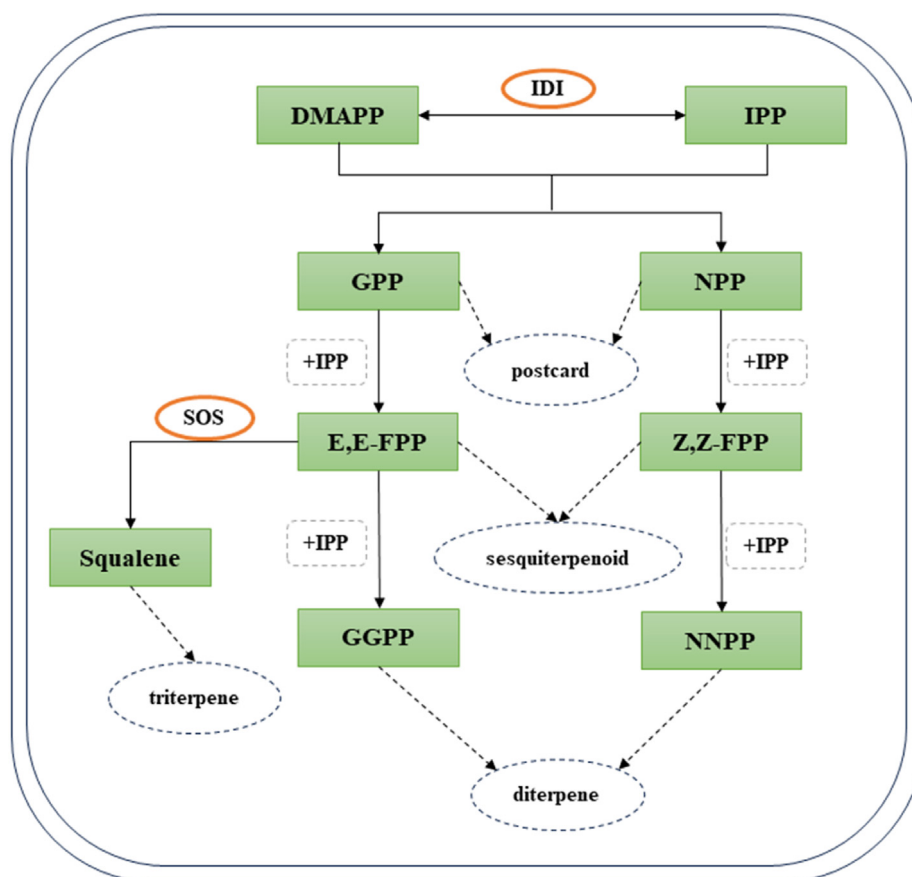


Fig. 4. Biosynthetic pathway of triterpenes and tetraterpenes

medicinal plant biosynthesis metabolism, can be involved in plant drought tolerance by regulating the synthesis of compounds such as flavonoids and anthocyanins. Shukla et al. experimentally demonstrated that *Scutellaria baicalensis* Georgi SbMYB15 overexpression in tobacco resulted in a significant enhancement of transgenic tobacco resistance to drought stress;<sup>50</sup> similarly *Paeonia lactiflora* Pall transcription factor PlMYB108, when overexpressed in tobacco plants, resulted in a significant increase in its flavonoid content, which increased its tolerance to drought stress;<sup>51</sup> MYB transcription factors, by regulating the expression of downstream genes to enhance the ROS scavenging ability has also become an effective way for medicinal plants to cope with drought stress, and it was found that *Betula platyphylla* Sukaczew overexpressing the *BpMYB123* gene showed stronger drought tolerance compared to RNA interference (RNAi) *Betula platyphylla* Sukaczew, and under drought stress, the activity of antioxidant enzymes was increased, which reduced the accumulation of ROS and malondialdehyde, and the plants showed stronger drought tolerance;<sup>52</sup> overexpression of *Fagopyrum tataricum* (L.) Gaertn transcription factors FtMYB9 and FtMYB13 was able to enhance *Arabidopsis thaliana* resistance to drought.<sup>53,54</sup>

#### 4.2. MYB TFs response to salt stress

MYB transcription factor copes with salt stress by enhancing the antioxidant capacity of medicinal plants. Heterologous expression of the *Ipomoea batatas* (L.) Lam transcription factor IbMYB308 in tobacco and salt stress treatment revealed that the expression of several antioxidant enzyme-related genes was up-regulated, CAT activity, POD activity, proline content was increased, and MDA content was decreased, and the transgenic tobacco with heterologous expression of the fava *IbMYB308* gene showed enhanced salt tolerance.<sup>55</sup> MYB transcription factors can also regulate downstream gene expression to enhance plant salt

tolerance. It was found that *Setaria italica* overexpressing the SiMYB16 gene had significantly higher flavonoid and lignin content and fatty acid synthase activity than the wild type under salt stress treatment. qPCR analysis revealed that the genes encoding its related genes in the lignin and chondroitin synthesis pathways were up-regulated in *SiMYB16* transgenic plants, indicating that the *SiMYB16* gene can regulate the expression of lignin and chondroitin biosynthesis positively regulating salt stress tolerance in cereals.<sup>56</sup> The modification of MYB proteins also plays an important role in salt stress response. MtMYBS1 of *Medicago truncatula* is highly expressed under salt stress, which consequently leads to a decrease in the level of DNA methylation of its promoter and the 3' end of the gene, and an increase in the level of H3K9ac modification of histones in the promoter region and near the translation initiation site, thereby enhancing salt tolerance.<sup>57</sup>

#### 4.3. MYB TFs response to other stresses

MYB transcription factors have important roles in the response of medicinal plants to UV-B light. MYB4R1 can regulate the accumulation of flavonoids and anthocyanins in plants in response to UV-B by binding to the L-box motifs in the promoters of the flavonoid and anthocyanin biosynthesis pathway genes, *FtCHS*, *FtFLS* and *FtUGT* in *Fagopyrum tataricum* (L.) Gaertn,<sup>58</sup> MYB transcription factors are also involved in the response to high temperature stress in medicinal plants, and the activation of the LIHSC70 promoter activity of *Lilium brownii* var *viridulum* Baker LiMYB305 is involved in the plant's heat tolerance in response to heat stress;<sup>59</sup> MYB transcription factors also play an important role in responding to low phosphorus stress, and low phosphorus conditions can induce the up-regulation of SmMYB98b expression in *Salvia miltiorrhiza* Bunge to promote the biosynthesis of tanshinones.<sup>60</sup>



#### 4.4. Role of MYB TFs in the regulation of hormone responses in medicinal plants

Phytohormones are indispensable substances that regulate various physiological and biochemical responses in plants so that life activities can be carried out normally. MYB transcription factors are involved in the regulation of a variety of biological processes, and are usually associated with phytohormones despite the complexity of the signalling pathways. *Rosa* sp R2R3-MYB gene *RhMYB108* is involved in ethylene- and JA-induced petal senescence. JA and ethylene induce the expression of *RhMYB108*, which directly binds to the promoters of *RhNAC053*, *RhNAC092*, and *RhSAG113* and facilitates their expression, and petals turn on the process of senescence;<sup>61</sup> *AaMYB1* overexpression in *Artemisia annua* L activates the expression of genes encoding key enzymes of the artemisinin biosynthesis pathway, *CYP71AV1*, *ADS*, *FDS*, *DBR2*, and *ALDH1*, especially *ADS* and *CYP71AV1*, which increases artemisinin synthesis; meanwhile, *AaMYB1* activates the expression of GA biosynthesis pathway enzyme genes, *GA3ox1* and *GA3ox2*, which improves GA synthesis, and then promotes the development of glandular hairs, and the density of glandular hairs was positively correlated with the content of artemisinin.<sup>62</sup>

One of the ways in which plants combat adversity in the growth process is through hormone signalling in the body to regulate hormone levels in order to adapt to changes in external factors and continue to survive. It has been found that transcription factors regulate the expression of corresponding functional genes in response to hormone signalling, which is an important part of plant growth, development and metabolism in response to adversity, and that this response is a mixed process of gene-signalling pathway-gene product interactions and feedback. In response to exogenous MeJA signalling, the expression level of *Salvia miltiorrhiza* Bunge transcription factor *SmMYB97* was increased, and it could directly bind to the promoters of tanshinone and salvianolic acid biosynthesis enzyme genes *SmPAL1*, *SmTAT1*, *SmCPS1* and *SmKSL1*, activate their expression, and promote the synthesis of tanshinone and salvianolic acid. Conversely, when the concentration of JA is low, the JA signalling pathway repressor *SmJAZ8* interacts with *SmMYB97*, inhibiting the transcriptional activation activity of *SmMYB97* and affecting the synthesis of tanshinone and salvianolic acid;<sup>63</sup> *Panax ginseng* C. A Mey *PgMYB2* is induced by MeJA, with an up-regulation of its expression level, and it can directly bind to the key enzyme gene dharmadendrol synthetase (*PgDS*) in the synthesis of ginsenoside promoter and activate its expression, promoting the synthesis of ginsenosides;<sup>64</sup> the transcription factor *TcMYB29a* from *Taxus wallichiana* var. *chinensis* (Pilger) Florin responded to the induction of ABA, with up-regulated expression levels, and subsequently regulated the expression of paclitaxel biosynthesis-related genes, *TcTS*, *TcT5OH* and *TcD-BTNBT*, which improved the synthesis of paclitaxel in suspension cultures of *Picea abies* cells;<sup>65</sup> and *CmMYB2* from *Chrysanthemum × morifolium* Ramat plant salt stress regulation all functioned through ABA dependence;<sup>66</sup> the *Artemisia annua* L R2R3-MYB transcription factor *AaTLR1* interacted with the positive regulator of glandular hair development, *GL3(bHLH)*, and inhibited glandular hair development; meanwhile, *AaTLR1* inhibited glandular hair development by recruiting the WUSCHEL-like protein, *WOX1*, which interacted with the LFY-family transcription factor *AaTLR2* interacts to form the *AaTLR1-WOX1-AaTLR2* protein complex, which inhibits the transcriptional activation activity of *AaTLR2*; *AaTLR2* is a positive regulator of GA synthesis, which promotes the development of the glandular hairs; ultimately, *AaTLR1* and *AaTLR2* impede the development of the glandular hairs through the inhibition of GA synthesis, which in turn decreases the synthesis of artemisinin.<sup>67</sup>

#### 5. Conclusions and outlook

The active components of medicinal plants are usually low in the plant body and are mostly produced or accumulated by plants under biotic and abiotic stresses. Whether or not specific secondary metabolites

are synthesised in plants, and in what amounts, is mainly determined by the expression of multiple synthase activities in their biosynthetic pathways, which are regulated by the corresponding transcription factors.

As one of the large transcription factor families in plants, the MYB transcription factor family is prevalent in plants and is involved in a variety of plant metabolic regulatory processes. However, most of the research on MYB has been focused on agricultural crops and fruits and vegetables, and relatively few studies have been conducted in the field of medicinal plants. In recent years, with the development of biotechnology, more and more studies on the structure and function of MYB transcription factors have been carried out, but the research on the active components regulated by transcription factors in medicinal plants is still in its infancy, and the main limiting factor is that the biosynthetic pathways of the majority of medicinal plants have not yet been clarified.

This paper reviews the role of MYB transcription factors in flavonoids, terpenoids and other compounds that are secondary metabolites of medicinal plants. It also reviews the role of MYB transcription factors in response to abiotic stress and in hormone signalling in medicinal plants. Therefore, for the study of traditional Chinese medicine, attention can be focused on the study of the effect of MYB-like transcription factors on the secondary metabolic process of medicinal plants as well as secondary metabolites, which will help to advance the study in depth, thus bringing into play the greater medicinal value of the plants and helping the traditional Chinese medicine to further fulfil its role.

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#### CRediT authorship contribution statement

**Xi Huang:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Quan Yang:** Writing – review & editing, Visualization, Investigation, Data curation. **Hongyang Gao:** Supervision, Project administration, Funding acquisition.

#### 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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