

Review

DNA methylation as the most important content of epigenetics in traditional Chinese herbal medicine

Mohamad Hesam Shahrajabian^{1,2#}, Wenli Sun^{1,2#} and Qi Cheng^{1,2#*}

¹Biotechnology Research Institute, Chinese Academy of Agricultural Sciences, Beijing 100081, China.

²Nitrogen Fixation Laboratory, Qi Institute, Building C4, No.555 Chuangye Road, Jiaxing 314000, Zhejiang, China.

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Traditional Chinese medicine is commonly used in China and so many other Asian and western Countries. Epigenetics relates to heritable alternations in chromatin architecture that do not involve changes in the underlying DNA sequence but profoundly affect gene expression and impact cellular function. Epigenetic regulation is attained by specific mechanisms involving DNA methylation, histone posttranslational modifications and the action of noncoding RNAs. Epigenetic variations also involved in the control of plant developmental processes and contribute in shaping phenotypic plasticity to the environment. Epigenetics has considerable impact on evolution and epigenetic epidemiology which has shown the intricate function between the environment and epigenetics. DNA methylation is an epigenetic mechanism that regulates gene expression and may affect plant growth, development and acclimation. DNA methylation is associated with gene expression and morphological variation. Plants, utilization of the epigenetic approach are used to manage and resist the fungal, bacterial and others biotic stresses; microbes, also employ epigenetic mechanisms to modify growth and pathogenicity, leading to resistance against plant-host immune system. DNA methylation is a chemical modification process where the methyltransferase (DNMTs) are catalyzed by selective addition of methyl groups to form 5-methylcytosine in CpG sequences. A mixture of herbs and fruits used in traditional Chinese medicine maybe use to decline diseases by adding and removing epigenetic marks on DNA. Epigenetics has been introduced to the area of TCM recently, which resulting in the hypothesis of an epigenetic role in the modern pharmacology of TCM prescriptions. Epigenetics is the partial material basis of TCM syndrome diversity, and the microscopic index of epigenetics can be an important supplement to the macroscopic syndrome differentiation of TCM syndromes. The role of epigenetic information is in developmental gene regulation, natural variation of gene expression levels, and response to the environment. The significant attention has started about the potential for epigenetic information to contribute to heritable variation in many species, even traditional Chinese herbs.

Key words: DNA methylation, epigenetics, traditional chinese medicine.

INTRODUCTION

Traditional Chinese medicine, epigenetics and DNA methylation

Traditional Chinese medicine (TCM) uses natural products, chiropractic, acupuncture and a combination of these subjects in a therapeutic course (Ogbaji et al.,

2018; Shahrajabian et al., 2018; Shahrajabian et al., 2019a; Shahrajabian et al., 2019b; Shahrajabian et al., 2019c). The recognizing of the molecular mechanisms of epigenetic inheritance is growing significantly. It has been reported that epigenetic modifications, including DNA methylation, histone post-transcriptional modifications,

micro RNA interference and etc, may help explore the molecular basis of Chinese medicine (CM) syndrome classification, and mechanisms of Chinese herbal medicine (CHM), CHM compounds and Chinese herbal formulae activities (Hu and Su, 2016). The mutual characteristics of Chinese medicine (CM) theory and epigenetic cognition is shown in Figure 1. The mutual characteristics include of 1) holism-integrity of environment, emotion, and diet with human body; 2) reversibility and balance of yin-yang and epigenetic modifications; 3) dynamic natures and epigenetic changes; 4) visceral manifestation and CM syndrome originated from epigenetic genotype. Epigenetics is considered to be a potential link between postnatal environmental factors and diseases, which refers to a reversible and heritable change that handles gene expression without any alter in the DNA sequence (Yao et al., 2018). An increasing number of epigenomes are now being investigated on crops of high economic value. Three types of known epigenetic mechanisms consist of DNA methylation, histone modifications, and small non-coding RNAs that regulate gene expression (Jirtle and Skinner, 2007). DNA methylation changes have been reported to be involved in the onset of a variety of metabolic diseases, like diabetes mellitus, fatty liver, and metabolic syndrome (Wang et al., 2015; Yara et al., 2015; Marfil et al., 2019). DNA methylation is one of the most important modifications of DNA nucleic acids, and it is considered as one of the most important epigenetic control mechanisms of gene expression (Serman et al., 2006). DNA methylation happens in many key physiological processes that including X chromosome inactivation, imprinting and the silencing of germline-specific genes and repetitive elements (Zhang, 2015). Plants are a powerful system for studying DNA methylation and epigenetic phenomena (Niederhuth and Schmitz, 2017). In plants, as in mammals, changes in DNA methylation are remarkable during reproduction and in reproductive tissues, a topic that has been reviewed elsewhere (Kawashima and Berger, 2014). Most important DNA methylation in plants comes from the study of one species, *Arabidopsis thaliana*, but it should be rapidly expanding to other species, especially traditional Chinese herbs and fruits (Zhang et al., 2018). Methylation has been found in all plant genomes, and certain pathways have been found to predominate and others to be defective (Niederhuth and Schmitz, 2017). DNA methylation is mediated by the family of DNA methyltransferases (DNMTs) that catalyze the transfer of a methyl group from S-adenosyl methionine (SAM) to cytosine of DNA (Wirbisky-Hershberger et al., 2017). DNA methylation suppresses the expression of harmful

DNA sequence such as endogenous retroviral genes that have been integrated into the host genome during evolution (Jaenisch and Bird, 2003). Cytosine methylation plays important roles in development and stress resistance in plants (Yang et al., 2018). The levels of genomic DNA methylation in plants are coordinately regulated by both methylation and demethylation (Chinnusamy and Zhu, 2009; Deleris et al., 2016). Methylation levels can change within repeats and transposons themselves depending on the particular transposon family (Eichten et al., 2012) and potentially also its age (Maumus and Quesneville, 2014). Mutual characteristics of CM theory and epigenetic cognition is shown in Figure 1. A model of the holistic and long-term therapeutic effect of TCM prescriptions is presented in Figure 2. Patterns of epigenetic marks such as DNA methylation (red) and histone acetylation (green) help maintain the gene expression profile for normal cell functioning. Aberrations in the epigenetic pattern, due to endogenous or exogenous factors, lead to disorders. Compounds in TCM medicinal (TCMFs), in particular the Monarch, interact with the epigenetics-related protein and the epigenetic pattern, once restored, is passed on to the daughter cells, the holistic (in contrast to reductionist's single gene or pathway) an long-term effects of TCM prescriptions are realized (Hseih et al., 2011).

ROLE OF EPIGENETICS AND DNA METHYLATION IN CROP IMPROVEMENT

There is the potential for epigenetics to play an important part in crop improvement strategies including the selection for favorable epigenetic states, creation of novel epialleles, and regulation of transgene expression (Springer, 2013). Cabej (2019) mentioned that epigenetic factors are determinants of the transgenerational plasticity in plant. He has concluded that a correlation is observed between the new acquired traits that appear as a result of transgenerational inheritance and specific epigenetic modifications, but it is not easy to determine whether these modifications are cause or effect of another unknown cause. Gallusci et al. (2017) stated that intense breeding has eroded genetic diversity, and epigenetic diversity now emerge as a new source of phenotypic alterations to improve adaptation to changing environments and ensure the yield and quality of crops. In spite the fact that, the mechanism of epigenetic regulations is a complex process, because of advances in gene expression mechanisms, many molecules for modulation of epigenetics will be recognized. Huang et al. (2017) found that epigenetic control of gene expression

*Corresponding author. E-mail: chengqi@caas.cn. #All authors contributed equally to this research.

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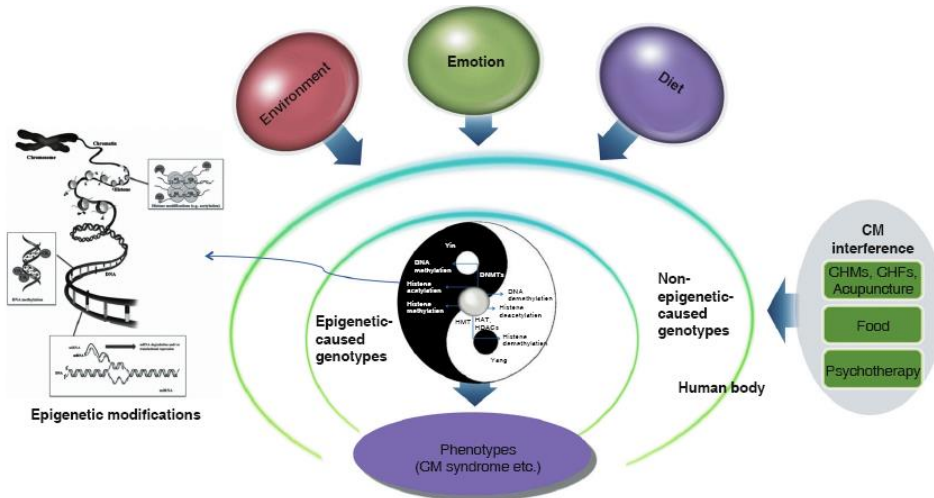


Figure 1. Mutual Characteristics of CM Theory and Epigenetic Cognition. Source: Hu and Su (2017).

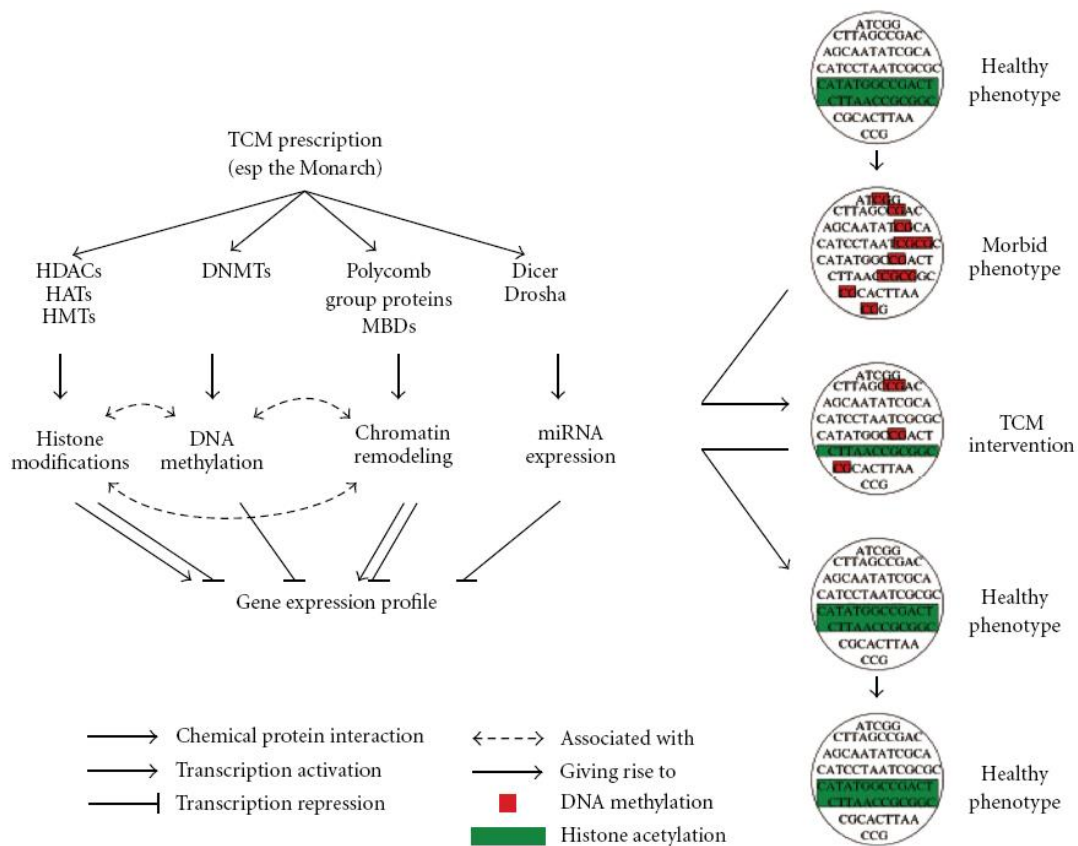


Figure 2. A model of the holistic and long-term therapeutic effect of TCM prescriptions.

encompasses the context of genes relative to DNA methylation, chromatin structure, and transposable element content. The epigenetic changes do not consist

of changes in the actual DNA sequence and consist of an ever-expanding array of other epigenetic processes mediated by prions, Polycomb protein, and higher-order

Table 1. Key terminologies.

Epigenetics: Heritable modifications in gene function without any involvement of the DNA sequence.
Epigenome: Set of chemical molecules and proteins that can bind to DNA to lead to activities turning genes on/off and regulating the proteins synthesis in certain cells.
Epigenomics: Study of the whole set of epigenetic alterations (epigenome) on the hereditary material of a cell.
Epigenetic marks: The modifications to the DNA and/or histones that causes epigenetics impacts including methylation, acetylation, ubiquitination, phosphorylation, sumoylation and poly (ADP) ribosylation.
Priming: memory of an internal and/or external cellular stimulus exposure that enables a plant to respond in quick and effective manner during future encounters.

Source: Barozai and Aziz (2018).

chromatin organization, as well as many others (Tollefsbol, 2017). Yao et al. (2018) suggested that the potential risk for metabolic disorders in individuals with phlegm-dampness constitution (PC) and also they did explain the clinical features of PC with DNA methylation features. Sorghum tissue methylation profiles produced at lower resolution using methylation-sensitive amplified polymorphism revealed similar findings, with insignificant methylation changes across seven tissues except for the endosperm (Zhang et al., 2011). The endosperm possessed genome-wide hypomethylation, which concurs with studies on *A. thaliana*, rice, and maize endosperm. Cao et al. (2019) demonstrated that DNA methylation influenced the transcriptional expression of Sclerostin (SOST) gene, which probably may play a vital role in the pathogenesis of primary osteoporosis. More et al. (2016) concluded that DNA methylation plays a meaningful role in gene regulation during growth, development and also different stresses. They have also indicated that DREB (Dehydration-responsive element binding) gene might be part of methylation events in transgenic plants by regulating certain regions of the plant genome that plays important role during stress conditions. DNA methylation mainly depends on two pathways: maintenance and de novo methylation. DNA methyltransferase (MET) and chromomethylase (CMT) are two key enzymes for maintenance methylation (Zhang et al., 2018). DNA methylation has been considered an underlying mechanism for temporary changes in plant phenotypes; also, DNA methylation is carried out by DNA methyltransferases that catalyse the transfer of a methyl group from S-adenosyl-L-methionine to cytosine bases in DNA, and cytosine methylation primarily appears in both CpG and CpNpG sequences (Hu et al., 2014). Key terminologies is presented in Table 1.

Gady et al. (2017) reviewed four epigenetic-based regulations in each phase of the tomato fruit set, development and ripening. Those regulations were included: (1) modifications in histone proteins, (2) methylation and demethylation of DNA, (3) regulation of significant locus by small RNAs through post-transcriptional processes, and (4) lncRNA (long non-coding RNA)-associated regulatory pathways. Cytosine

DNA methylation levels have been found positively correlated with the root growth through determining the role of salicylic acid (SA) on the methylation patterns and plant development in four pearl millet (*Pennisetum glaucum*) varieties (Ngom et al., 2017). Farinati et al. (2017) reviewed in detail the role of significant epigenetics parameters in rosaceae for about three important fruit developmental processes. Crisp et al. (2016) presented a detailed review on the plants' response processes involved in recovery from stresses through epigenetics regulations including resetting to memory development. Recently, Secco et al. (2017) reviewed in detail some of the advancement on involvement of histone modifications, histone variants and DNA methylation in response to nutrient stresses. Epigenetics' regulatory tools of gene expression are also vital for plants survival especially when they are exposed to biotic stresses such as bacteria, viruses, fungi, parasites, insects and weeds (Barozai and Aziz, 2018). Dubey and Jeon (2017) explained in detail the host epigenetic modifications during *Magnaporthe oryzae* pathogenesis progress and host-pathogen interactions, while suggesting the role of epigenetics in the epidemiology for future research and studies. A mode depicting in the involvement of DNA methylation in fruit ripening is shown in Figure 3. In immature fruit, numerous genes associated with ripening have methylated promoters, which inhibit RIN targeting and subsequent transcriptional activation. In an uncharacterized manner, the promoter regions become demethylated during ripening stages and corresponding genes experience binding by RIN and active transcription, triggering fruit ripening. The *cnr* mutant inhibits the demethylation process and prevents fruit ripening (Ji et al., 2015). The model of regulation of secondary metabolism by DNA methylation is shown in Figure 4.

Wei et al. (2014) proved that the correlating changes of cytosine methylation and proteomic expression were evidenced under cold treatment in *Brassica napus*. Duan et al. (2018) found that all of the major epigenetic mechanisms in mammals also occur in plants. Niederhuth and Schmitz (2017) concluded that methylation as well as the pattern of that methylation

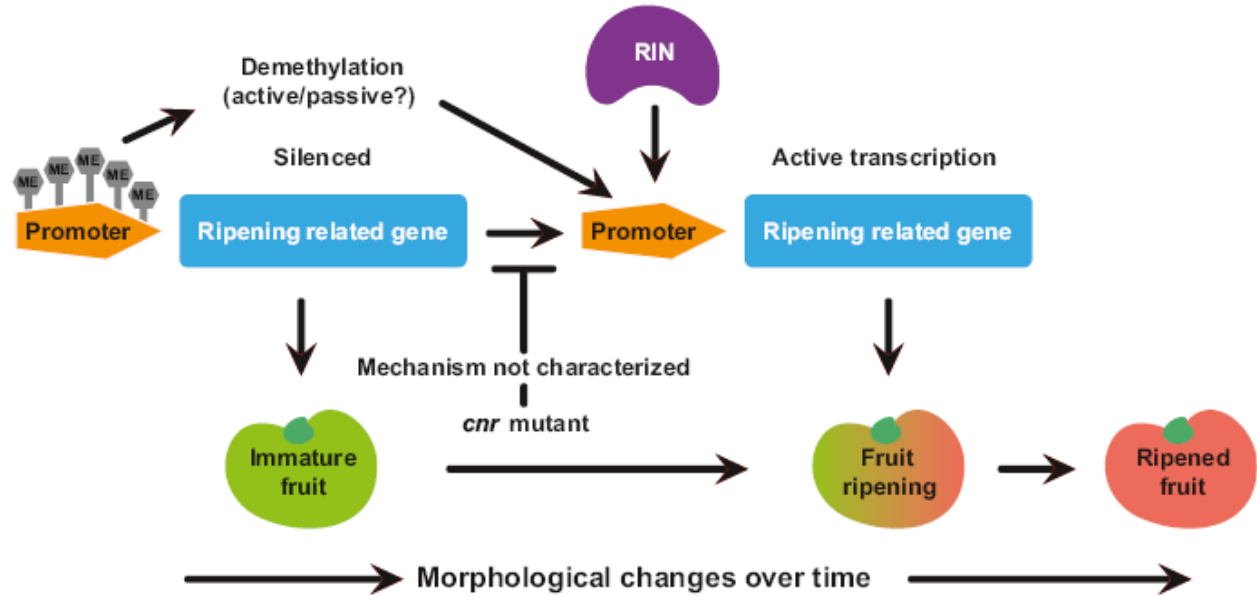


Figure 3. A mode depicting the involvement of DNA methylation in fruit ripening.

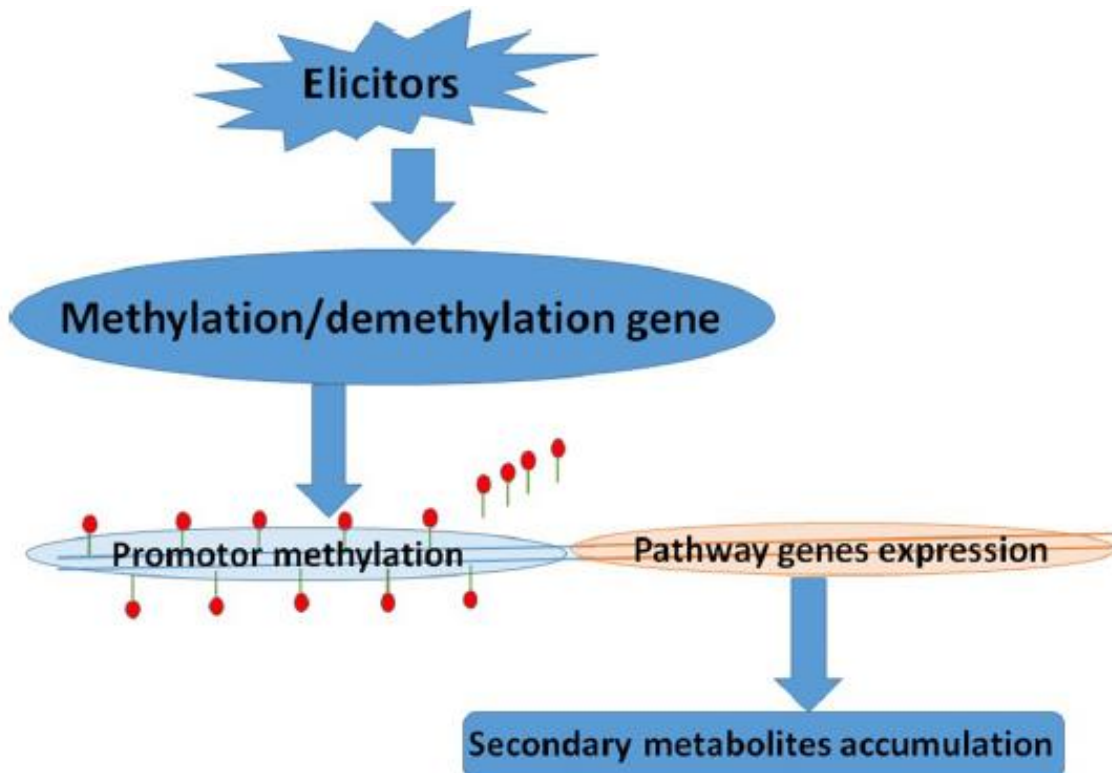


Figure 4. The model of regulation of secondary metabolism by DNA methylation. Source: Yang et al. (2018).

within or outside of the gene is highly dependent upon the type of methylation. Hsieh et al. (2011) reported a further support for the notion of the epigenomes as a

drug target and a new set of tools for the design of TCM prescriptions. Amarger et al. (2014) found that dietary compounds containing methyl group donors are important

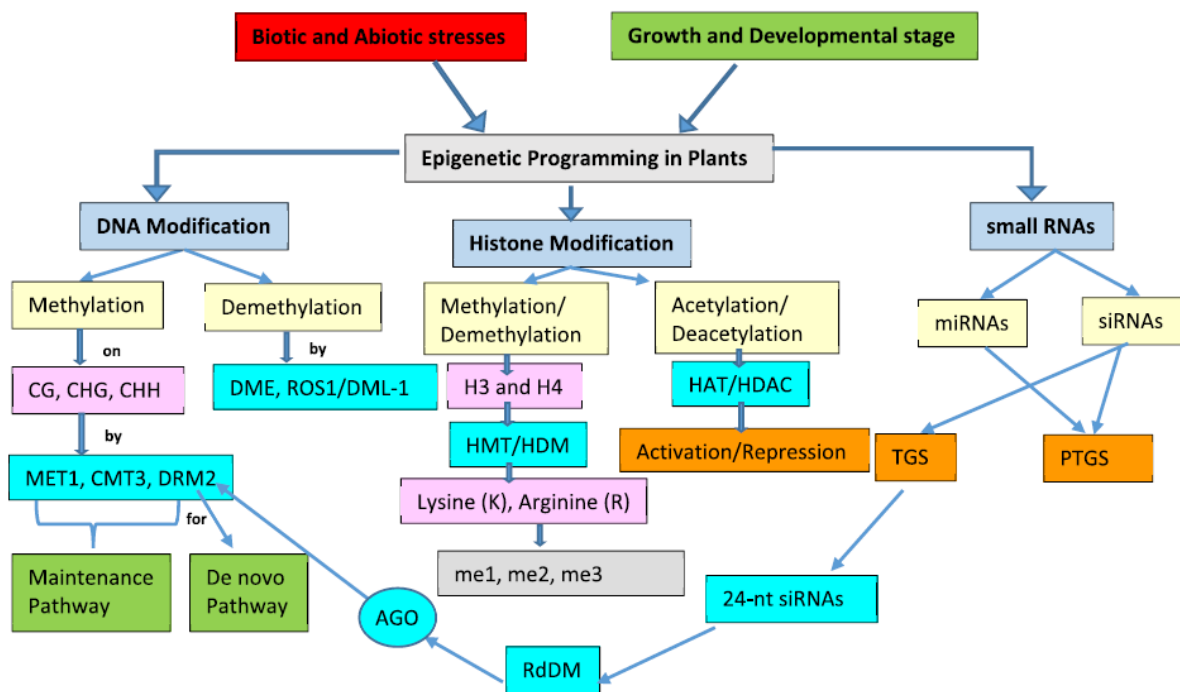


Figure 5. Detail description of epigenetics programming under biotic and abiotic stresses as well as for growth and development in plants. AGO= Argonaut, CG= Cytosine Guanosine, CMT3= chromomethylase 3, DME= Demeter, DML-1= Demeter- like 1, DRM2= domains rearranged methyltransdarase 2, H = A, C or T, H3= Histone 3, H4= Histone 4, HAT= histone acetyl transferase, HDAC= histone acetyl deacetylase, HDM= histone demethylase, HMT= histone methyl transferase, me1= one methyl, me2= two methyl, me3= three methyl, MET1= methyl transferase 1, miRNAs= microRNAs, PTGS = posttranscriptional gene silencing, RdDM= RNA-directed DNA methylation, ROS1= Repressor of silencing 1, siRNAs= small interfering RNAs, TGS= transcriptional gene silencing. Source: Barozai and Aziz (2018).

regulators of nuclear DNA methylation. Wang et al. (2016) revealed that sequence analysis of the fragments that underwent changes in DNA methylation or gene expression indicated that these changes were associated with various biological pathways. They have suggested that alternations in DNA methylation caused by hybridization and polyploidization may induce changes in gene expression and lead to new agronomic traits in polyploids. Liu et al. (2018) indicated DNA methylation-regulaed auxin pathways plot a role in establishing inbred depression phenotypes in plant. Vargeer et al. (2012) reported that DNA methylation appears to have a direct effect on the severity of negative inbreeding phenotypes. Xiao et al. (2006) stated that DNA methylation regulates gene transcription over large regions of the genome, and can be maintained throughout life cycles and over various generations. Yang et al. (2018) announced that DNA methylation regulates the expression of key genes involved in phenolic acids biosynthesis to affect phenolic acids production in *Salvia miltiorrhiza*. They have also reported the roles of DNA methylation on phenolic acids accumulation will provide new perceptions on the regulation of secondary metabolism in plants. Detail description of epigenetics programming under biotic and

abiotic stresses is presented in Figure 5. Plant epigenetics programming under stress managements and growth related stages are shown here, at three levels: DNA modification, Histone modification and small RNAs. The boxes colors are showing symmetry in explanation, mode of action, epigenetics types, processes and players involved in these processes. The plasticity during growth and development as well as under biotic and abiotic stress management is depicted via the routes of DNA modification, Histone modification and generating small RNAs (Barozai and Aziz, 2018).

Mastan et al. (2012) revealed that the (Methylation sensitive amplification polymorphism (MSAP) analysis showed that under salt stress homologous nucleotide sequences in genome from control and salt treated plants of *J. curcas* showed different patterns of methylation; which suggest that these fragments probably an important role to induce immediate adaptive responses in *Jatropha* under salinity stress. Li et al. (2015) revealed that NiCl₂ application caused variation of DNA methylation of the *Arabidopsis* genomic and offspring's. NiCl₂ also resulted in nucleolar injury and deformity of root tip cells; the methylation rate of 18S rDNA also changed by adding NiCl₂. Dossa et al. (2018) observed

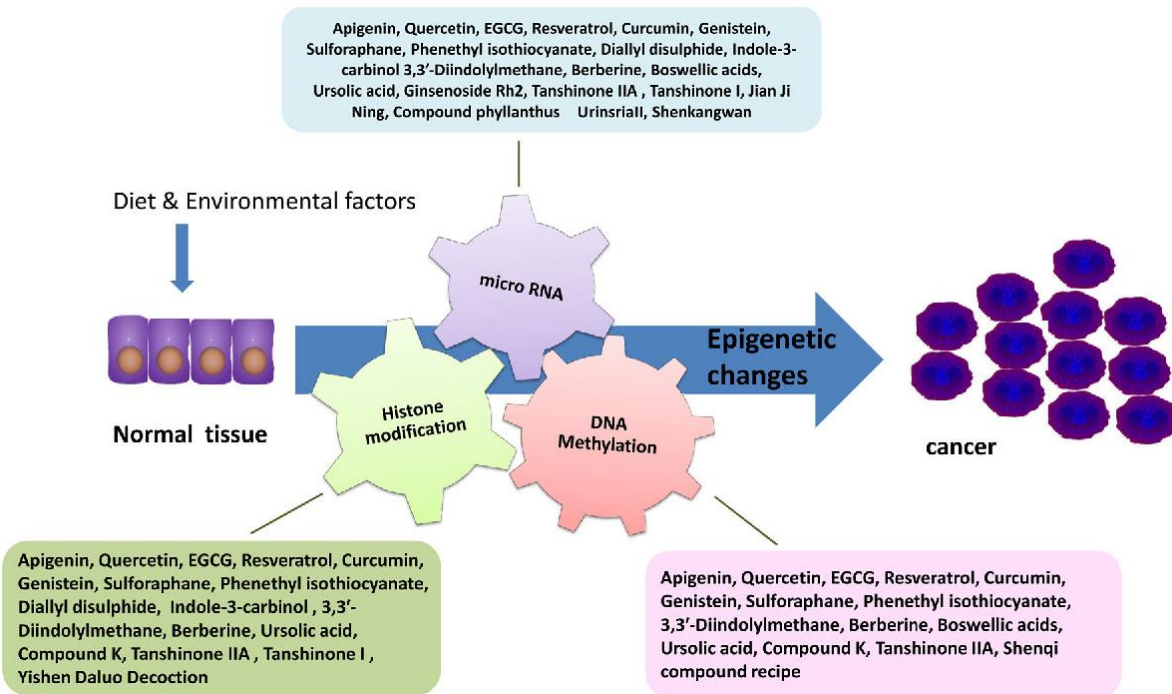


Figure 6. Potential epigenetic mechanism of phytochemicals in traditional Chinese herbal medicine for cancer prevention.

Source: Zhou et al. (2017).

that sesame has divergent epigenetic programs that respond to drought and waterlogging stresses and an interplay among DNA methylation and transcript accumulation may partly modulate the contrasting responses to these stresses. Wang et al. (2011) indicated that demethylation of genes is an active epigenetic response to salt stress in roots at the seedling stage, and helps to further elucidate the implications of DNA methylation in crop growth and development. Arikian et al. (2018) demonstrated the mutual interaction between morphophysiology, DNA methylation and the associated gene expression, and provide insight into the abiotic stress response of *Arabidopsis*. Li et al. (2015) described that cultivated ginseng maintained high levels of genetic and epigenetic diversity, but showed distinct cytosine methylation patterns compared with wild ginseng high methylation level and polymorphism reported could be related with the high structural genome plasticity which has been reported in the *Brassica* species to explain the phenotypic variability of this species. Zhao et al. (2010) suggested that the demethylation positively contributed to salt tolerance and the hypermethylation had negative influence on salt tolerance in cotton. Peng et al. (2007) showed that the methylation mutation involved into the whole rice genome and the 12 pairs of chromosomes; the mutation trend was site-related and there were different mutation loci for different triploids, which foretold that SARII-628 would have different evolution fates after

natural homologous triploidization. Chen et al. (2014) suggested that DNA methylation maybe involved in the sterility-fertility transition of PA64S under two different environmental conditions. Underwood et al. (2017) concluded that DNA methylation profiling of hundreds of natural *Arabidopsis* accession has revealed that transposable elements exhibit significant intraspecific genetic and epigenetic variation, and that genetic variation often underlies epigenetic variation. Lu et al. (2008) demonstrated the power of the MSAP (methylation sensitive amplification polymorphism) technique for large-scale DNA methylation detection in the maize genome, and the complexity of DNA methylation change during plant growth and development. They have concluded that different methylation levels maybe related to specific gene expression in various tissues. Epigenetics has the ability to impose flexible growth in plants depending on the conditions prevailing so that deciphering such regulation may enable designing stress-tolerant crops (Banerjee and Roychoudhury, 2017). Potential epigenetic mechanism of phytochemicals in traditional Chinese herbal medicine for cancer prevention is shown in Figure 6. Correlation of epigenetic regulators with salinity and drought is shown in Table 2.

Epigenetic modifications, including DNA methylation, histone post-transcriptional modifications, micro RNA interference and etc. may help explore the molecular basis of Chinese medicine syndrome classification, and

Table 2. Correlation of epigenetic regulators with drought and salinity.

Stress	Epigenetic regulators	Functions	Relation with stress tolerance
Salinity	ADA2b	Transcriptional adaptor	Positive
	HDACs (HD2C, HDA6, HDA19)	Histone deacetylase	Positive
	HDA705	Histone deacetylase	Negative (seedlings)
	HDT701	Histone deacetylase	Positive (seedlings)
	AtROS1	Demethylase	Positive
	SW13B	Chromatin remodeler	Positive
Drought	ATX1	Histone methyltransferase	Positive
	MSI1	Silencer	Negative
	MYST, ELP3, GCN5	Histone acetyltransferase	Positive
	AtHD2C	Histone deacetylase	Positive
	CHR12	Chromatin remodeler	Negative
	BRM	Chromatin remodeler	Positive

Source: Banerjee and Roychoudhury (2017).

mechanisms of Chinese herbal medicine (CHM), CHM compounds and Chinese herbal formulae activities (Hu and Su, 2017). Hu and Su (2017) concluded that Chinese medicine (CM) and epigenetics might promote each other and jointly develop following the continuous progress of epigenetics in Chinese medicine researches. Zhou et al. (2017) stated that the progress of epigenetic alternations in cancer, emphasizing the role of traditional Chinese herbal medicines (TCHMs) as potential preventive/therapeutic agents for cancer management, and provides a basis and potential future direction for the development of novel therapeutic drugs. Zhai et al. (2016) reported that epigenetic regulation may provide some innovative research ideas for finding new drugs of the treatment of diabetes from traditional Chinese medicine and natural medicine. DNA methylation is a reversible process by the removal of methyl groups and this property makes DNA methylation a promising drug target to treat cancer (Easwaran et al., 2014). Ou et al. (2009) found that a set of genes encoding for the various putative DNA methyltransferase, 5-methylcytosine DNA glycosylases, the *SWI/SNF* chromatin remodeler (DDM1) and siRNA-related proteins are extremely sensitive to perturbation by spaceflight, which might be an underlying cause for the altered methylation patterns in the space-flown plants. Hsieh et al. (2013) concluded that TCM prescriptions' modulation of the human epigenome help elucidation of phyto-pharmacology and discovery of epigenetic drugs. Furthermore, as TCM medicinals' properties are closely tied to patient TCM syndromes, results of this material-medicinal-wide, bioinformatic analysis of TCM medicinal may have implications for molecular differentiation of TCM syndromes. Different traditional Chinese medicine has been shown to be safer and more fruitful for preventing cancer by targeting epigenetic landscape (Hun Lee et al., 2013). Yang et al. (2016) expressed that targeting epigenetic genes can be a promising plan to

treat hematopoietic system malignancies and TCM is attractive to explore drugs targeting epigenetic modifiers.

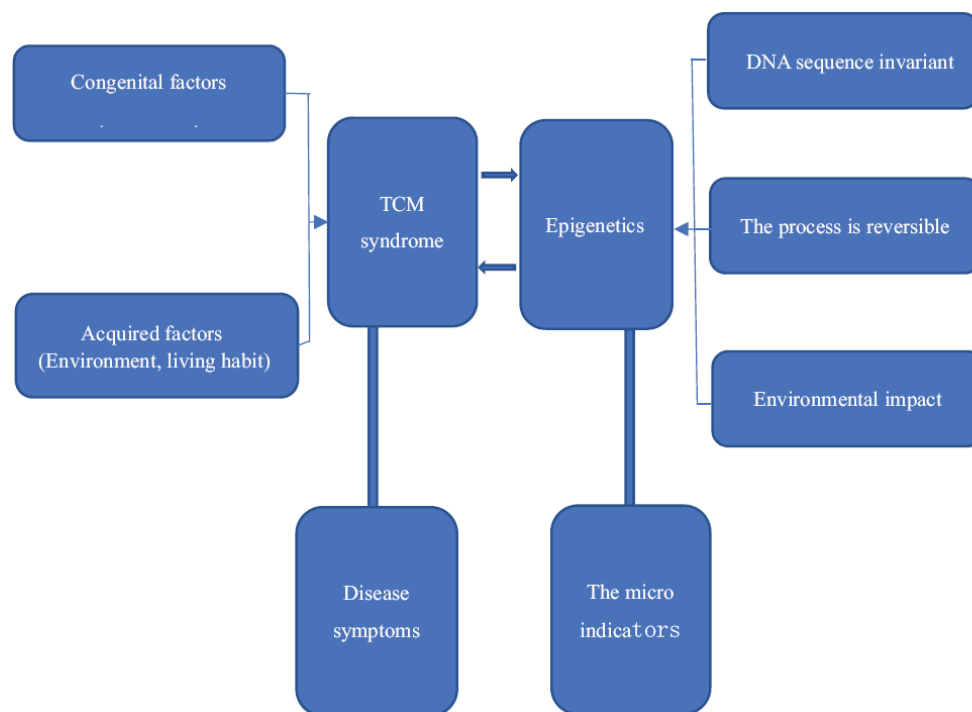
TRADITIONAL CHINESE MEDICINE AND DNA METHYLATION

Some scientists have proposed that epigenetics is the partial material basis of TCM syndrome diversity, and the microscopic index of epigenetics can be a necessary supplement to the macroscopic syndrome differentiation of TCM syndromes. So, the correlation between epigenetics and TCM syndromes phenotypes is considered as one of the key scientific problems to realize the breakthrough of TCM clinical practice. Ma et al. (2018) indicated that DNA methylation-miRNA-Target gene is the main line, which further reveals the essence of TCM syndrome. To improve the level of TCM clinical syndrome differentiation and the clinical efficacy of TCM, especially in the study of RCM syndromes of chronic hepatitis B (CHB), discovering its underlying biological signature is necessary. Correlation between TCM syndromes and epigenetics is shown in Figure 7. Epigenetics is the partial material basis of TCM syndrome diversity, and the microscopic index of epigenetics can be a necessary supplement to the macroscopic syndrome differentiation of TCM syndromes (Ma et al., 2018). Integrative medicine (IM), routes and effects is presented in Figure 8. The figure represents how IM works at different levels such as the psychological, physiological, biochemical and/or epigenetic levels. The red arrows indicate the different initial levels at which IM can exert its action so that the final action is exerted at the epigenome. An altered epigenome then produces beneficial effects at different levels indicated by green arrows. The epigenetic regulations of TCM on tumors have been shown in Table 3. An IM approach can

Table 3. The epigenetic regulations of TCM on tumors.

Targets	TCM or TCM active ingredients	Effects
DNMTs	Trichosanthin	↓DNMTs activity in human breast cancer MDA-MB-231 cells
	Tanshinone IIA	↓DNMT1 in HepG2 human hepatoma cells
	Arsenic	↑DNMT1 and ↓p16 in human hepatoma cells
	Trioxide	↓↓DNMT3B in leukemia HL-60 cells
	Yugan granule	↓DNMT1, ↓DNMT3A and ↓DNMT3B in mice hepatoma cells
	Genistein	↓DNMTs activity and ↑ p16 in KYSE 510 cells
	Curcumin	↓Histone H3 acetylation in Raji, HL-60 and K562 cells ↓HDAC1 activity in HepG2 human hepatoma cells
Histone modifications	Triptolide	↓SUV39H1 and EZH2 in multiple myeloma RPMI8226 cells
	Epigallocatechi n-3-gallate (EGCG)	↓HAT (histone acetyltransferase) activity in androgen-dependent prostate cancer cells
	Gernistein	↑Tumor suppressor genes (PTEN, CYLD, p53 and FOXO3a), remodeling the heterochromatic domains of their promoters in prostate cancer cells

Source: Yang et al. (2016).

**Figure 7.** Correlation between TCM syndromes and epigenetics.

Source: Ma et al. (2018).

work at these different levels through a specific hierarchical sequence, or at different levels simultaneously. Some approaches can first act directly at the epigenetic level, surpassing the psychological and physiological levels. After the alteration of the epigenetic profile, the effect can manifest in the form of gene expression and biochemical changes, physiological

and/or psychological changes (Kanherkar et al., 2017). Direct, indirect and combined epigenetic pathways of integrative medicine is shown in Figure 9. The figure represents a summary of the epigenetic mechanisms underlying different IM approaches. The cell is represented as oval pink structure with a yellow nucleus. The fine structure of chromatin comprised of DNA

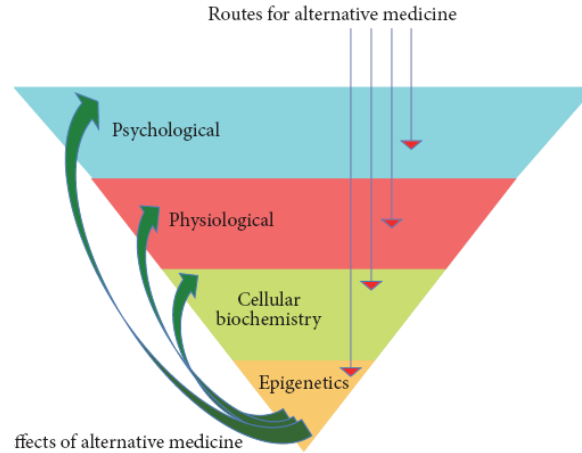


Figure 8. Integrative Medicine (IM): routes and effects. Source: Kanherkar et al. (2017).

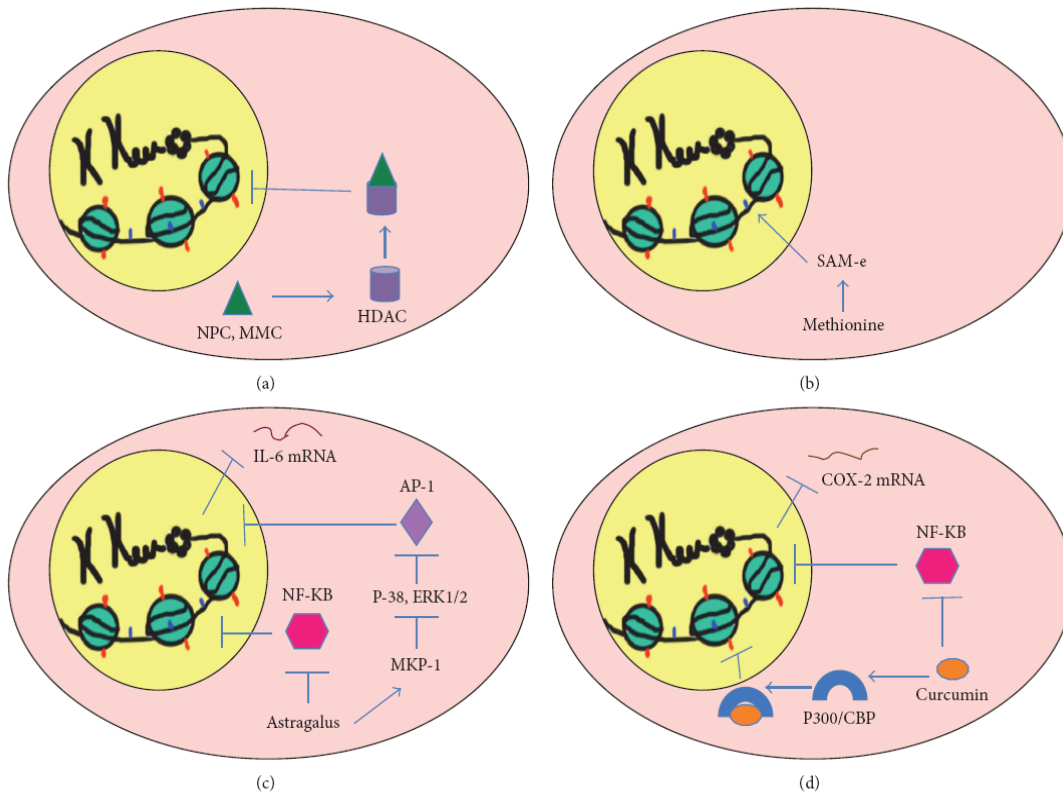


Figure 9. Direct, indirect, and combined epigenetic pathways of integrative medicine (a) Type 1 direct pathway: Traditional Chinese Medicine (b) Type 2 direct pathway: herbal methionine (c) Indirect pathway: Astragalus (d) Combined pathway: curcumin. Source: Kanherkar et al. (2017).

wrapped around histones in the nucleus is the ultimate regulatory components through which IM approaches manifest their outcomes. Red marks on histones represent acetyl groups on histone tails (histone acetylation) and blue marks represent methyl groups on

DNA (DNA methylation). (a) Type 1 direct pathway: Traditional Chinese Medicine. Traditional Chinese Medicine (TCM) compounds like Ningposides C (NPC) and Monomethylcucumin (MMC) (represented by green triangles) act as HDAC2 (represented by purple cylinder)

inhibitors that inhibit deacetylation of histones and relax the chromatin structure. The mode of action of NPC and MMC is through a Type 1 direct pathway since they directly interfere with the epigenetic enzyme HDAC. (b) Type 2 direct pathway: herbal methionine. Dietary compounds like herbal methionine (HM) that donate methyl groups and increase SAME levels in the body are important regulators of nuclear DNA methylation. An increased production of SAME from HM increases the bioavailability of methyl groups (metabolite) that contribute to the constitution of epigenetic tags, specifically affecting DNA methylation levels. Thus, HM follows the Type 2 direct pathway by interfering with the bioavailability of compounds that constitute epigenetic tags. (c) Indirect pathway: Astragalus. Astragalus extract has anti-inflammatory properties and can promote its effects through two different pathways. Firstly, it inhibits p38 MAPK and ERK1/2 via stimulation of MPK that in turn blocks the nuclear translocation of AP-1 (lavender diamond) responsible for expression of proinflammatory cytokine IL-6. Secondly, it interferes with the nuclear translocation of NF- κ B (pink hexagon) and inhibits NF- κ B-mediated transcription that in turn activates proinflammatory genes. Thus, Astragalus follows an indirect epigenetic pathway by interfering with cellular signaling pathways. (d) Combined pathway: curcumin. Curcumin (Orange oval) possesses anti-inflammatory activity that operates through a combination of direct and indirect pathways. Through the direct epigenetic pathway, it specifically inhibits a specific p300/CBP HAT (blue semicircle) thereby reducing histone acetylation and through the indirect epigenetic pathway it blocks pathways involving the transcription factor NF- κ B (pink hexagon) that in turn block the production of COX-2. Thus, curcumin operates through a combination of direct and indirect pathways (Kanherkar et al., 2017). Hao and Xiao (2018) reported that the epigenetic and epigenomic mechanisms should be highlighted in the study of specific phenotype and indigenosity of geoherbals. They have stated that revealing the correlation between epigenetics and geoherbs could shed light on the quality assessment, authentication, molecular breeding and sustainable utilization of medicinal plants and the associated microbes. Vidalis et al. (2016) indicated that the concept of epigenetics should be introduced into the geoherb studies, and the role of DNA methylation. China and adjacent regions possess spectacular ecosystem diversity, which partially determines the epigenetic diversity and is the ecological basis of geoherb diversity (Huang and Chen, 2017).

CONCLUSION

Traditional Chinese medicine has contributed to human health care for thousand years and it is still popular not only in Asian countries, but also in western societies.

TCM is a system of both theories and therapies that was first documented in ancient Chinese classics dating back 2100 years. Epigenetics, combining genetics and environment contributes to not only the stability of organisms but also their adaptability to the environment, which is consistent with the theory of human-environmental inter relation of TCM. Epigenetics consists of heritable modifications in gene function without involvement of the DNA sequence. Epigenetic mechanisms are involved during all stages of a plant, from flower to mature seed for reproductive organs, development that determined crop productivity and seed nutritive traits. Epigenetics is a hot research topic in recent years and DNA methylation is the most common and the most studied epigenetic content. DNA methylation may lead to variations in gene expression without changing its DNA sequence. In plant, many epigenetic changes, mainly at the level of DNA methylation, are transgenerational stable and contribute to formation of epialleles, affecting developmental and agronomical traits. Plants traditional Chinese herbs and fruits are suitable for studying epigenetics, and also opens the possibility for utilizing or inducing epigenetic differences for purpose of plant breeding and improvement. Epigenetics of traditional Chinese herbs offers a strong support for the proposition of an epigenetic role in TCM pharmacology. Epigenetic regulation has been recognized as an important player in the response to changes in key environmental conditions such as light, temperature and drought. Epigenetics' regulatory tools of gene expression are important for plants survival especially when they are under various stresses like bacteria, viruses, fungi, parasites, insects and weeds. The epigenetic-based programming in plants under biotic and abiotic stresses as well as during growth and development is carried out by methylation-demethylation, acetylation-deacetylation and small RNAs, which are involved in the regulation of gene expression without any change in the DNA sequences. Various traditional Chinese medicine has been shown to be safer and more effective for preventing cancers. Plants' utilization of the epigenetic approach are used to manage and resist the fungal, bacterial and others biotic stresses; microbes, also employ epigenetic mechanisms to modulate growth and pathogenicity, leading to resistance against plant-host immune system. DNA methylation is a chemical modification process where the methyltransferase (DNMTs) are catalyzed by selective addition of methyl groups to form 5-methylcytosine in CpG sequences. A mixture of herbs and fruits used in traditional Chinese medicine maybe use to alleviate diseases by adding and removing epigenetic marks on DNA. Epigenetics has been introduced to the area of TCM recently, which resulting in the hypothesis of an epigenetic role in the modern pharmacology of TCM prescriptions. Epigenetics is the partial material basis of TCM syndrome diversity, and the microscopic index of epigenetics can be a

necessary supplement to the macroscopic syndrome differentiation of TCM syndromes. All in all, in conclusion, new agronomical plans and adaptive agronomical practices are needed to face the future increase in food demand resulting from expanding population.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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