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Review Article

Serum Pharmacochemistry in Herbal Medicine and Its Active Ingredients: Current Evidence and Future Development

Abstract

Traditional Chinese medicine (TCM) is more and more increasingly concerned all over the world based on its multiple ingredients, multi-target, effectiveness and hypotonicity. However, the fuzzy cognition of the effective ingredients of TCM has been the fundamental reason that hinders its development due to complexity and uncertainty.

For the sake of modernization of TCM, discovering the effective ingredients of Herb Medicine (HM) or TCM formulae as the markers of the inner quality control is urgent now. Luckily, the new technologies and methods are more applied for discovering the active constituents of HM or TCM formulae. In the context of the effective ingredients which are absorbed into blood, the method of serum pharmacochemistry of TCM (SPT) has been considered as a rapidly and effective tool to investigate the effective constituents. Therefore, one of the purposes of the review is to make it easier to understand and apply the theory of SPT by meaning of briefly introducing some strategies, key technologies and recently applications. Secondly, it is necessary for SPT to integrate with metabolomics based on its inherent disadvantages, in addition, network analysis and Q-Marker will be referred as the new directions to better develop SPT, it is not only for comprehensive control of quality of HM and TCM formulae, but also for the modernization and internationalization of TCM.

Introduction

TCM has been widely used for relieving pain, adjusting immune function of organism, saving people's life, being an alternative therapy, attracting the interest of the world. It consists of multiple kinds of constituents including alkaloids, flavonoid, triterpene, glycoside and so on. Several different kinds of herbal medicines in form of TCM formulae are commonly applied for many diseases or TCM syndromes, like Rheumatoid Arthritis [1], Breast Cancer [2], Diabetes Mellitus [3], Alzheimer's disease [4], chronic bronchitis [5], whose pharmacological effects are demonstrated through many active constituents acting on different targets [6-10], which has been proved effective in countless cases during thousands of years in China and other countries [11]. The phenomenon that people are willing to choose TCM formulae as their first choice comparing with Western medicine is often the case in China to some degree. Not only that, nearly 42% of all new drugs are more and less derived from active compound of the natural medicinal plants from 1981 to 2014, just like TCM [12].

But with the international development of TCM, there has been a series of huge obstacles in the process due to unclear and ambiguous effective compounds based on the extremely complexity property [13,14]. What are the effective constituents of TCM? And how do we discover them rapidly? Which are vital cases for modernization of TCM? In other words, these are the major blockage to understand and reveal the mystery of herbal medicines because of the lack of awareness in effective material basic and biological disposition [15]. It is the time for us to build a reliable approach to discover the effective constituents and further to establish overall quality control standards of TCM to promote the modernizations and internationalization of TCM.

TCM applies a multiple components and multiple targets approach for the treatment of diseases instead of single constituent, single target, which determines the complexity of TCM research. Although the traditional pharmacological methods of separation and screening of active ingredients are feasible, such as the successful example of artemisinin, there is no denying that this method is a waste of time and the

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final result maybe show that it's not effective in vivo [16,17]. Differently, the constituents who transfers into the blood after administration are more likely to be considered as the effective ones, which was first proposed by Japanese scholar in 1989, the hypothesis that only the absorbed ingredients are able to take effect in the targets has been widely accepted by more and more scholars all over the world [18-20]. Based on the theory, fortunately, in early 1990s, Professor Wang first proposed a novel way which embodies drug action, absorption, distribution and interaction with the organ is used to rapidly screen effective ingredients of TCM—serum pharmacochemistry of traditional Chinese medicine (SPT) [21]. The theory and content of SPT are defined as "Based on the classical research methods of medicinal chemistry, using modern separation technology and multidimensional detection, analysis, identify or characterize the constituents absorbed into the blood in animal models or human beings, elucidating the active compounds which are bound up with the efficacy, finally, determine the basis material of TCM [22]. Not only can it establish a practical and quick method for globally analyzing the constituents in vitro, but also the prototype and metabolites in vivo from HM and TCM formulae with the aim to discover active compounds [21-24]. What is worth mentioning that it is not the end to draw the conclusion of these concerned potential active constituents from the normal animals models, but on the condition of specific disease or syndrome, further to analyze the change process of absorbed constituents in the blood and organs, only do absorbed ingredients meet the requirement of "detectable, fast absorbed, slow elimination, comparatively higher concentration and maintaining the longer time" and further verified by pharmacodynamics tests, they can be deemed to be real effective constituents [21,25].

Until now, the method of SPT is getting more and more accepted by Chinese scholars, which has been playing a significant role in elucidating the effective constituents more than twenty years [26-28]. This paper will focus on impacts on effective constituents' discovery through SPT method including some strategies, key technologies and recently applications, in addition, some problems found in practice and the direction of SPT's development will be explained, too.

Technologies and strategies

It is well known that TCM has adopted prominent biological activities by many active compounds due to interacting with numerous targets and regulating a series of transduction pathways [29]. The reason why their popularity has been receded is that the sensitive and selective analytical techniques are lack in the past of 20 years [30]. Beyond that, although some nature compounds are detected in vitro, the questions involved the low absorption and interference of endogenous substances are tough to overcome in blood samples from animals models or human beings [29].

Fortunately, ultra-high-performance liquid chromatography (UPLC) has developed into the most common device for analyzing biological samples based on the reverse-phase liquid chromatography (RPLC), it has a high separation capacity as well as analysis time is shortened because of the ultra-high-pressure infusion pump [31,32]. Compared with HPLC, UPLC has advantages over it where its high-resolution capability can narrow the peak width and enhance the signal-to-noise ratio, thus UPLC are more suitable for the analysis of biological samples [33]. For the sake of feature of high sensitivity, superiorities of speed, and wide dynamic range over other techniques, mass spectrometry (MS) has been applied so much [34-36], mass spectrometry-based analytical methods are playing a vital role in science research [37], in particular, the analysis of biological samples. Capillary, electrophoresis, liquid chromatography, and gas chromatography, which can be coupled with MS [38-41]. LC-MS has been shown to be a practical tool in-rapidly screening of the chemical substances, which integrates both advantages of LC and MS that global detection and identification of nontargeted components are desirable in natural product research [42-44]. Based on these situations, LC/MS and LC/MS/MS are available for being used in research of SPT. Moreover, MS/MS provides precise structure identification that the ingredients can be characterized directly without the reference standards [45]. It offers unique structure identification of compounds whether the components in mixtures even in only trace amounts or not, it can quickly provide the fragment information you want [46,47]. Furthermore, some literature reported that UPLC-MS offered a versatile tool that is accompanied with enhanced throughput that makes it the optimum tool for analyzing plant extracts, phytochemical substances, their main metabolites and it can shorten analysis time even though the samples are the complicated constituents of TCM and biological samples [48,49]. The approach of UHPLC-ESI-TOF-MS is widely used for the development of the serum pharmacochemistry [18,27,28,50]. With the development of technology, UPLC coupled with TOF-MS and even UPLC-ESI-Q-TOF- MS/MS has been generally accepted to be a good technique for analyzing of multiple constituents and metabolites in vivo owed to high mass solution and accurate mass measurement at present [48,51,52,53]. It turns out that the effective ingredients in biological samples after dosing have been founded successfully by adopting this technology in recent years [11,12,15,19].

For the study of SPT, multivariate data processing approach (MDPA) has an indispensable effect which is capable of establishing a practical means for rapidly screening and identifying the bioactive ingredients in TCM between the control and dosed group [18,28,50,54-56]. It's not hard to summarize this train of thought as follow: All LC/MS raw data including retention time, accurate mass, and MS/MS spectra are exported into MarkerLynx software (Waters Corporation, Milford, USA) for preprocessing at first, peak picking, normalization, deconvolution, then, the three-dimensional data is acquired into the EZinfo software(Waters Corp, Milford, MA,USA) to be analyzed with principal component analysis (PCA) and orthogonal partial least-squared discriminant analysis(OPLS-DA) in the next step. PCA can visually gain the details of differences between the two groups, which shows the differences caused by exogenous ingredients transported into the blood. Sample name, tR-m/z pair and icon intensity output by OPLS-DA, subsequently, an S-plot will be generated which was used to visualize the compounds dedicating to the discrimination.

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In addition, the ions present only in dosed group and absent in the blank group are output easily by using VIP-plot deprived from OPLS-DA, among them, the ions furthest away from the origin have a higher value of VIP concerned significantly contributing to distinguish the two different groups. Next, the molecular formula and accurate molecular mass of potential constituents need confirming by means of Elemental Composition tools of MassLynx™ software. Then, check the database to initially identify them, but the precise identification needs to comparing MS/MS fragment icon by Mass Fragment™ application manager. In order to further confirm the resource of the metabolites of absorbed constituents, some scholars are willing to choose software named Metabolynx XS version which owns a full-scale range of the potential biotransformation reactions with the elemental compositions of every possible metabolites as possible as it can. Expected and unexpected metabolites are given automatically by elimination of the interfering peaks after comparing the blank samples [57,58]. It does good for us to verdict the structure and the resource of the metabolites. It is reported that Metabolynx™ software with mass defect filter (MDF) technique has been applied for screening the metabolites to identify the possible metabolites in the biological samples but not in blank samples based on MSE spectra as soon as possible [59]. In addition, under the MSE mode, fragment information of compounds without optimized the collision energy individually can be given [60-62].Flow chart of active compound study guided by SPT (Figure 1).

Recent applications

In recent years, a large number of research publications has showed that serum pharmacochemistry of TCM has made a great progress in discovering the active constituents from HM or TCM formulae. The applications of SPT are listed in table 1. Ju characterized the absorbed ingredients in rat plasma after dosing of saponins from the leaves of Panax notoginseng by establishing UPLC-Q-TOF-MS/MS method, compared with blank and dosed plasma samples, the result showed that 22 ingredients were detected and identified including 17 prototype constituents as potential effective components. Based on this research, the author further researches the pharmacokinetic of saponin in rats after dosing. The result indicated that all saponins displayed a long duration in plasma with a t1/2 longer than 15 h, except for notoginsenoside Fe (t1/2=2.78 h)[63];

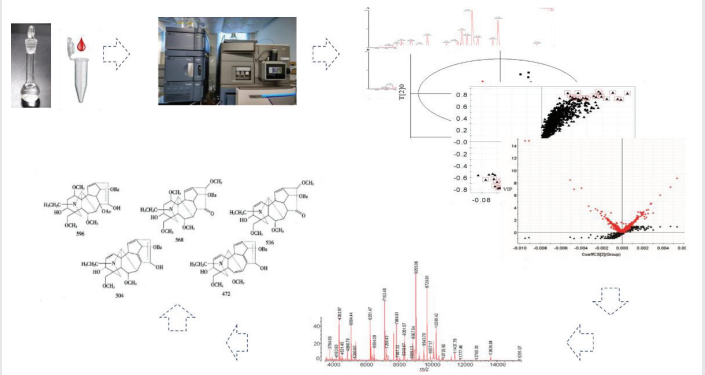

Figure 1: Flow chart of active compound study guided by SPT.

Table 1: Recent Applications of SPT in TCM

Name	analytical method	detected components	Reference
Acanthopanaxsenticosus Harms Leaf	UPLC-Q-TOF-MS	131 compounds tentatively	[22]
AcanthopanaxSenticosus stem	UPLC-Q-TOF-MS	115 compounds in vitro;41 compounds in vivo	[21]
Acanthopanaxsenticosus fruit	UPLC-Q-TOF-MS	104 compounds in vitro;24 compounds in vivo	[48]
HuangqiGranule	HPLC-DAD_ELSD	calyco-sin-7-O-β-D-glucoside, ononin, calycosin, astragaloside IV, and formononetin	[38]
saponins from leaves of Panax notoginseng	UPLC-Q-TOF-MS	22 ingredients in vitro;17 prototype constituents in vivo	[46]
Radix Polygalae	UPLC-Q-TOF-MS	6 prototype components ;7 metabolites	[40]
Radix Astragali	HPLC-MS	astragalosidI, astragaloside II, astragalosideIII, and astragalosideIV	[50]
Mouten Cortex	UPLC-Q-TOF-MS	16 parent components in vitro;7 metabolites in vivo	[49]
TongmaiYangxin Pill	UPLC-Q-TOF-MS	40 potential bioactive compounds	[13]
Shenfudecotion	UPLC-Q-TOF-MS	19 ginsenosides; 16 alkaloids	[51]
Da-Bu-Yin-Wan	UHPLC–ESI-Q-TOF-HD-MS/MS	22 absorbed prototype; 16 metabolites	[12]
Zi Shen wan	UPLC-Q-TOF-MS	22 prototype components ; 11 metabolites were identified in vivo	[37]
Sanziguben Granule	UPLC-Q-TOF-MS	gallic acid and corilagin	[52]
Zeng Ye Tang	HPLC-Q-TOF-MS/MS	Catalpol, harpagide,p-coumaric acid, harpagoside, angorosideC, cinnamic acid	[56]
DangguiShaoyaoSan	HPLC-DAD	paeoniflorin, albiflorin, ferulic acid and alisol B 23-acetate	[53]
Zhi-Zi-Da-Huang-decoction	UHPLC-FT-ICR-MS	10 prototype compounds . 4 metabolites from Gardenia jasminoides Ellis, and 3 prototype and 1metabolite from Citrus aurantium L	[57]
GuizhiFuling capsule	UPLC-Q-TOF-MS	6 prototype compounds ;9 metabolites	[41]
Xiang-Fu-Si-Wu Decoction	UPLC-Q-TOF-MS	102 chemical components ; 41 metabolites	[54]
Shengmai san	UPLC-Q-TOF-HDMS	23 prototype components; 7 metabolites.	[55]

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Apart from the examples above, Sun and her colleagues had a research on Acanthopanax Senticosus Harms stem, they found that 115 compounds were from the aqueous extract in vitro and 54 were discovered for the first time, of 41 compounds in vivo, including 7 prototype components and 34 metabolites by MDPA [27] .With the shortage of Acanthopanax plant resources, as a substitute of the root of Acanthopanax senticosus Harms, the extract of Acanthopanax senticosus Harms Leaf has been drew widely attention in recent years. In order to study whether the two have the similar active ingredients or not, Zhang made a preliminary exploration on Acanthopanax senticosus Harms Leaf, 131 compounds were characterized by UPLC-Q-TOF-MS as potential effective constitutes from the extract of the plants, such as, triterpenoid saponins, phenols, flavonoids, lignans, coumarins, and polysaccharides [28]. Different parts of the traditional Chinese medicine maybe have different effective constituents [64]. In Han's paper, he found 104 compounds of Acanthopanax senticosus fruit (ASF) in vitro and in total, among them, 24 prototype compounds were characterized by comparing the blank blood samples with the dosed group rat blood samples based on theory of SPT [65]. He made a series of immunological experiment including visceral index, the ability of the spleen cell proliferation, delayed-type hypersensitivity degree and so on to verify that ASF had the immunomodulation effect, as an initial observation, this is true, but it would be better if he could realize that certain components in the serum were truly effective only when given in the pathological state, unlike normal rats. The same author made a research on Radix Polygalae for screening the multiple constituents by UPLC-Q-TOF-MS/MS combined with MDPA in vivo as well as in vitro, in the end, 13 compounds were characterized involved six prototype components and seven metabolites which were discovered for first time [56]. The results can only be used as an initial study of active ingredients.

Mouten Cortex (MC) is widely applied to against allergic and inflammatory while what its effective constituents are in the blood are not clear now. On account of this reason, Liu established a method using UPLC-ESI-Q-TOF-MS technology based on the theory of SPT with MDPA to analyze the active constituents in rats after oral administration. The result showed 16 prototype components and 7 metabolites were discovered in vivo as potential effective constituents [66]. Like Chen's research, preliminary studies on the serum pharmacochemistry and pharmacodynamics of Huangqi Granules were performed from the water extract of it, he found that calycosin-7-O-β-D-gluoside, ononin, calycosin, astragaloside IV, and formononetin in rat blood after oral administrating using HPLC-DAD-ELSD. It's worth learning that the author first affirmed the water extract of Huangqi Granules was capable of good pharmacological effect through DPPH as well as MTT experiments. Then, began to research the effective ingredients [67]. In a word, what calls for special attention is that absorbed constituents by comparing blank group with dosed group are not the final effective ingredients for representing the quality of the TCM, only be they are verified effective by specific animal models and with appropriate pharmacokinetic parameters [17].

In order to research the bioactive components and pharmacokinetic of Tongmai Yangxin(TMYX) Pill, Fan utilized serum pharmacochemistry technique by UPLC/Q-TOF-MS to study the active ingredients of methanol extract of Tongmai Yangxin Pill , the results showed that 40 potential bioactive compounds were identified by comparing the chemical fingerprint of methanol extract, control serum and dosed serum, spectra with data in the publications, luckily, those ingredients have a variety of activities [19].The same technique was adopted by He, with the purpose of studying the material basis of Shenfu Decotion(SFD), He built a UPLC fingerprints of SFD at first, then serum samples were analyzed though MarkerLynx XS software. 19 ginsenosides and 16 alkaloids were successfully detected in SFD at last [68]. Recently, Li and her team had made some progress in Da-Bu-Yin-Wan. She took full advantage of high-performance liquid chromatography equipped with electrospray ionization quadrupole time-of-flight high-definition mass spectrometry to comprehensively screen and identify the effective compounds of methanol extract from Da-Bu-Xin-Wan in vivo by utilizing software of Masslynx (V4.1), 38 compounds were detected including 22 prototype and 16 metabolites in the blood after dosing of Da-Bu-Yin-Wan in total [18]. The same scholar, she had another research in Zi Shen Wan, which is a classical formulae applied to treat prostatitis and infection diseases. UPLC-MS with multivariate analysis approach was developed by Li to characterize the active constituents of it. Among them, 92 peaks in vitro and 33 peaks in vivo were characterized and further identified 22 prototype components and 11 metabolites deprived from 33 peaks [50]. To reasonably control the quality of Sanziguben Granule, Zhang adopted SPT theory to discover the effective ingredients. Profile of Sanziguben in vitro firstly was built by 15 batches, subsequently, blood samples were collected at four different moments. Finally, the changes of time of gallic acid and corilagin into the blood indicated the pharmacological significance and might be confirmed as the bioactive compounds of Sanzuguben Granule [69].

With the purpose of investigating the differences of material basis between blood-associated and water-associated herbs of DangguiShaoyaoSan (DDS), the research method of DDS was built by Zhang guided by the SPT theory. At first, he established the HPLC fingerprint of the formulae, and then the serum samples from sixteen groups were analyzed through HPLC-DAD, compared with the chromatogram and spectrogram of DDS and serum samples of sixteen, in the end, a conclusion that paeoniflorin, albiflorin, ferulic acid and alisol B 23-acetate in co-decoction were concerned as the active constituents of DDS was drawn [70]. ULPC-Q-TOF-MS method with MetaboLynx was applied for the primary investigation of metabolism pathway of active Xiang-Fu-Si-Wu Dection fraction, 15 constituents were identified, including six parent compounds and nine metabolites [71]. To screen and characterize of ingredients of Guizhi Fuling capsule (GFC) in vitro and metabolic profile of active constituents in vivo .UPLC-Q-TOF-MS-MS was used by Zhang, 102 chemical components were identified, 41 metabolites were characterized and needed to research pharmacological experiments to verify in the next step [57]. In the aspect of Shengmai San, Han and her colleague made some achievement, in their research, a method was adopted for the rapidly analyzing the metabolites

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of Shengmai San in rat plasma after oral administration. The result indicated 30 constituents were successfully identified, including 23 parent components and 7 metabolites [72].

Differently, Tian's team identified 50 ingredients in Zeng Ye Tang in vitro, then nine compounds were identified by 3T3-L1 adipocytes due to interacting with cells. Further, the potential effective compounds were detected in the blood through SPT analysis between normal and diabetic rats after dosing of Zeng Ye Tang, the result was that six shared prototype constituents had been verified to have anti-diabetic effects on type 2 diabetic mice, they were catalpol, harpagide, p-coumaric acid, harpagoside, angoroside C, cinnamic acid , some of which including harpagide, harpagoside, angoroside C, and cinnamic acid were from Xuanshen; catalpol, p-coumaric acid and acteoside were from Shengdi; methylophiopogonanone A and methylophiopogonanone B were from Maidong [73] .The similar mode of research was used by Han. In the literature, Han's team constructed a comprehensive way by using UHPLC-FT-ICR-MS and SPT technique to discover the effective compounds of Zhi-Zi-Da-Huang decoction (ZZDHD) which can detoxify hepatotoxicity in alcohol-induced rats after dosing. Before by comparing fingerprints of blank serum and drug-dosed serum, the blood samples were firstly investigated the hepatoprotective effect on BRL-3A cells, 18 constituents in vivo were secondly discovered to be the most potential effective ones in ZZDHD, and 10 parent ones and 4 metabolites were concerned to be from Gardenia jasminoides Ellis, and 3 parent ones and 1 metabolite from Citrus aurantium L [74]. In total, either the freeze-dried extract of Zeng Ye Tang from Tian or the serum samples of Han, we not only need to detect constituents of TCM formulae as many as possible in vitro but also obtain several active compounds related to therapeutic effect. In other words, the active compounds we get from multiple kinds of ways need to be verified by cell models or animal models in the pathological state. Here comes the question. According to the traditional Chinese medicine theory, the formulae is prescribed according to the doctor's diagnosis of patents' TCM syndrome, if we want to copy the animal models which are consistent with this clinical TCM syndrome, are there any inner index to verify that the models are successful? There seems to be something missing to tie them together.

Future development

TCM is the precious treasure and has made an indelible contribution to the development of the Chinese nation until now. But the quality of HM as well as TCM formulae is declining due to various reasons, for example, the environment, it is particularly important to quickly establish the quality standards of HM and TCM formulae to ensure the efficacy. SPT as a practical tool plays an increasingly vital role in rapidly screening active components, while it also has some disadvantages to overcome. As mentioned above, the potential active substances that we take for granted have all efficacy corresponding with TCM syndrome, isn't right? How to find the inner indicators of TCM syndrome to copy animal models? Luckily, metabolomics is the exactly best answer the perfect the theory of SPT.

Metabolomics was first put forward in 1999 as an important part of system biology by Professor Jeremy [75], it can be defined as a subject that research the organism in pathological and physiological state producing a series of reflection, including gene expression and environmental pressure and so on. No matter what and no matter how, metabolome is the end-product and most stable, which is an "omics" science that concentrates on the series of metabolites (molecules< 1k Da) in a biological system [76,77]. It is a powerful means to globally detect the metabolites to find biomarkers which can reveal the general metabolic conditions and even for underlying pathophysiology of diseases [21,78-80]. With the background, some scholars made many contributions to life science by metabolomics [81-86]. Recent years, metabolomics has been widely used to explore the mechanism of drugs [87,88]. Luckily, the traditional Chinese medicine also takes effect in a holistic way to regulate yin and yang to achieve the balance in forms of formulae with TCM syndrome under the guidance of TCM theory [89,90]. Based on the theory and research method of SPT at present, professor Wang further integrated with metabolomics to update the theory and research method named Chinmedomics. Taking the biological characters of TCM syndrome as a research starting point and formulae as object, a new platform which is able to directly discovered the efficacy material base of TCM was built. The metabolomics technology is used to reflect biological essence of disease or TCM syndrome in order to establish a biological evaluation system, like the animal model, while SPT is to fast screen the potential active substances transmitted into the blood after dosing. Representative endogenous biomarkers of disease or TCM syndrome have a relevance to exogenous constituents for discovering the constituents highly associated with efficacy of formulae, here bioactive constituents are by Chinmedomics [9,91,92,93].A sketch of the relationship between SPT and Chinmedomics as follows (Figure 2).

Recently, a lot of evidence showed that Chinmedomics has been playing an important role in comprehensively finding the material base of HM as well as TCM formulae. The literatures have been published in succession, such as Kai Xin San [94], Chuan wu [95], herbal medicine AS1350[96], gentianine [97], scoparone [98], berberine [99], nanshi oral liquid [55], Shen Qi Wan [100], ShenQi pill [101], Phellodendri Amurensis cortex [9], Yin-chen-hao-tang [102] and so on.

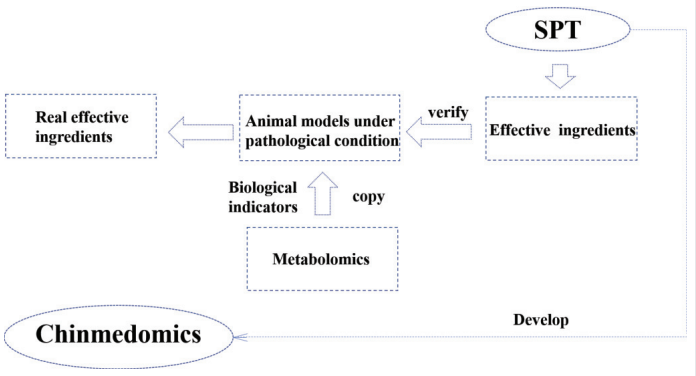

Figure 2: A sketch of the relationship between SPT and Chinmedomics.

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Q-marker of Chinese material medical is a hottest topic for evaluation and quality control in recent years. It was proposed by Academician Liu in 2016 intended to improve the quality of TCM and the level of quality control [103,104]. The definition of quality markers concentrates on unique Chinese medicinal materials differences, an overall quality control was established by dynamic changes and their transmission and traceability [105,106]. As a crucial part of the theory of Q-marker, quality transmission is the vital indicator to check the quality of TCM from in vitro and in vivo, especially, the constituents absorbed into body need to be detected by technical of serum pharmacochemistry [107]. Just like Zhang's essay, he and his teammates attempted to explore the effects of Shengmai San on Appswe/PSIdE9 mice model to identify the effective components which can be considered as Q-marker. The result showed that eight compounds may be considered as Q-Marker of SMS [108]. Coincidentally, the similar idea which was proposed by Yan appeared in another article considering that Chinmedomics is an effective tool to find Q-Marker, several examples were given to illustrate his opinion [109]. All the attempt of Chinmedomics can be effective to perfect the theory of Q-Marker for quickly screening the active indicator of TCM.

Network pharmacology was proposed by Professor Hopkins for the first time in 2007, which illustrates the occurrence and development of diseases from the perspective of system biology and biological network balance, as an area of bioinformatics is getting popularity now [110,111], while a network-based TCM research published by Li and his team was earlier than Professor Hopkins [112-114]. There's no doubt that the method of serum pharmacochemistry is being applied for network analysis for predicting the potential active components, text mining, similarity match, the constituents were employed by network pharmacology to identify the potential targets. These target proteins related with the key processes, pathways and related to diseases were analyzed by STRING database. In the end, the most possible targets of components obtained [115].

The same mode adopted by Zheng and his colleagues. In his paper, they concentrated on rhubarb treatment of renal fibrosis, the method of serum pharmacochemistry was used for the several rats' groups to elucidate the active compounds at first, based on it, subsequently, the network pharmacology method was to determine the interaction between the constituents and disease targets, the results that anthraquinones and flavanols were the main active components of rhubarb [116]. It could be another new direction to develop serum pharmacochemistry and to further rapidly explore the material basis, mechanism of TCM.

Conclusion

TCM has been widely used to protecting human health for thousands of years. Countless experiences have shown that they work. However, finding the effective substances from TCM is a tough case which must be overcome no matter how complicated and variable constituents of it. The review introduced briefly the theory of serum pharmacochemistry of TCM and outlined its technologies and strategies, recent applications of SPT including the herbal medicine and formulae, further explained the method to screen and identify the compounds in vitro as well as in vivo, comparing the blank and dosed blood samples by MDPA, then judging the parent substances and metabolites and further research the pathway of metabolites. Whereas there are some differences between the normal state and pathological state, such as enzymes, thus steps above are only preliminary results, they need to be verified by pathological models to prove their effectiveness. This sets the stage for metabolomics to reveal the essence of disease and syndromes, which makes the combination of SPT and metabolomics inevitable. The theory of SPT developed to be Chinmedomics which perfects the shortages of SPT to discover the real active compounds for more comprehensively controlling of the quality of TCM. In this paper, some new development directions have been introduced, such as Q-Marker and network analysis, which are to find the effective ingredients for establishing the overall quality control standard of TCM for realizing the standardization and international of TCM.

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