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中医方证代谢组学——中药效应评价的有效途径

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关键词
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摘要

有效性评价是发现中药药效物质基础、先导化合物和质量标志物的重要前提，因此急需建立一种生物学语言，将中药有效性科学地表达出来，进一步凸显中医药的实用价值。证候和方剂是中医药的重要组成部分，与中药有效性直接相关。我们以证候和方剂为研究对象，建立了科学评价中药有效性的创新方法学体系——中医方证代谢组学。它将中药血清药物化学理论与代谢组学技术有机整合，在解决证候生物标记物的基础上，建立方剂药效生物评价体系，发现并确认中药药效物质基础。该策略为提高中医理论和临床实践的科学价值提供了有力支持。本文概述了中医方证代谢组学的研究策略，利用该方法揭示临床常见中医证候生物标记物及开展相关方剂的有效性评价研究，着重阐述了中药药效物质基础及质量标记物的发现。

1. 引言

由于人类疾病谱的变化，单靶点、单一药物的简单治疗模式难以解决多靶点复杂性疾病的治疗问题[1,2]，个体化的精准治疗又对现代医学提出了新的挑战。多靶点作用的中药在复杂疾病的治疗中较单靶点药物具有独特优势[3–5]，中药的多靶点治疗及中医学辨证论治个体化治疗的精准潜力等在解决多靶点复杂性疾病治疗方面积累了大量有价值的临床经验。然而，中药有效性是中医治疗优势的根本体现，也是横在中医学与现代医学科学家之间难以逾越的鸿沟，致使中医学的优势及其临床经验的价值难以被充分接受。

中药有效性应该包括3个方面的内容，即临床效应、效应机制及效应成分。首先，中药有效性在临床上是以方剂为用药形式针对证候表达的，只有在精准辨证的基础上实现方证对应才能充分表达中药的临床疗效。任何超越了证候与方剂而研究有效性的方法都将与中医临床实践脱节[6]。从单味中药研究获得的结论必将由于配伍其他药物而改变，同一中药在不同方剂配伍环境下，在体内将表达（吸收）不同的成分，从而实现配伍的药效取向[7]。因此，研究中药有效性必须从证候和方剂入手，在方证对应状态下阐释效应、效应机制及效应成分。

由此，通过整合代谢组学与中药血清药物化学技术，以证候生物标记物发现为切入点，以方剂为研究对象，建

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立了集阐明效应、揭示效应机制及鉴定效应成分于一体的中药有效性研究的新策略——中医方证代谢组学（chinmedomics）[8]，即利用代谢组学技术发现并鉴定中医证候（病）的生物标记物，以生物标记物为参数评价方剂的临床疗效；在有效状态下，以中药血清药物化学技术分析鉴定方剂进入体内的显效成分，将其与证候生物标记物轨迹回调相关联，挖掘与生物标记物轨迹变化高度关联的进入体内的方剂成分，从而鉴定表达方剂临床疗效的药效物质基础并阐明其效应机制，解决创新药物设计、质量标记物发现、方剂配伍规律等与有效性相关的科学问题[9,10]（图1）。该理论及方法充分体现了中医辨证论治、方证对应的理论特点及临床实践的要求，为深度理解并挖掘中医理论的科学价值及中医临床经验的实用价值提供了新策略。

2. 中药有效性评价面临挑战

中医药的发展深受中国古代哲学思想的影响，包括在中医诊疗中有充分体现的阴阳学说、整体观、辨证论治等思想[11]。整体观与辨证论治是中医诊断及治疗疾病、提高临床疗效优势的基本特点[12]。中医治病用的是方剂[13]，而方剂对应的是证，证是中医对病的描述，基于众多的症状综合描述分析获得，涉及思维层面，缺少客观的标准，具有模糊性，且难以重现。由天然草药、动物、矿物质等按君臣佐使配伍原则组成的方剂，是中医药治疗疾病的基本形式。单味中药所含化学成分数以百计，由多种中药组成的方剂已成为高度复杂的化学巨系统，导致药效物质基础的确认困难重重。

众多中医学专家目前致力于中医药治疗优势的全球化发展。然而，由于中医理论的复杂性，其功效不能用现有的有限药理学指标来表达。现代医学家甚至是生命科学领域的科学家都难以认识并接受中医临床经验的实用价值。因此，对中医药疗效的科学解释已成为国内外医学科学家不可逾越的障碍，限制了中医药治疗优势和临床经验的充分利用。

在国际医学领域，中医的整体观及个体化治疗理念逐渐被认可[4,14]。然而中医证候的诊断和评价标准依赖个人总结经验和经典古籍描述，导致中医证候缺乏标准化、系统化和现代化，以及临床使用的客观性和标准化[15]。因此，中医药最新进展聚焦于如何表达方剂的物质基础和证候的科学内涵。诸如此类问题使中医药学的现代化发展停滞不前。

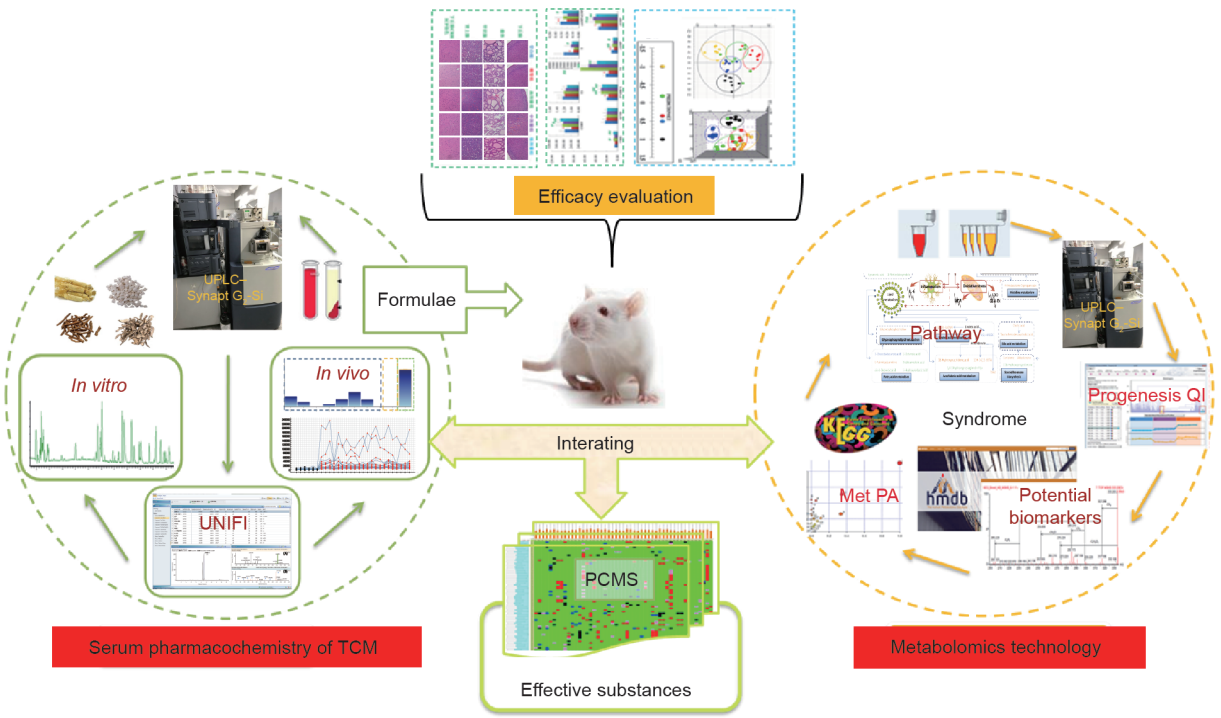

图1. 中医方证代谢组学：整合代谢组学与血清药物化学来评价中医药有效性的策略。PCMS：代谢物与血清成分的相关性分析；UNIFI：中药及天然产物发现和鉴定数据库。

3. 中医方证代谢组学——研究策略和技术

证候模糊性和方剂复杂性导致疾病诊断和有效性评价困难重重，并且极大地限制了中药有效成分的发现[16–19]。方剂有效性和证候生物学本质研究是中医药的重要科学问题。中药血清药物化学理论建立于20世纪90年代初，提供了发现中药在人体内的活性成分的方法，解决其相关疗效和安全性问题[20]。21世纪初，中药血清药物化学理论整合代谢组学方法构建了中医方证代谢组学创新策略，用于阐明证候本质和中药功效并发现其有效成分[21]。如前所述，中医方证代谢组学方法可揭示证候的候选生物标志物、相应方剂功效及药理机制，同时促进证候的精准诊断，挖掘临床治疗经验，为提高中医科学价值提供了有效策略[9,22,23]。

3.1. 代谢组学技术

尽管中药血清药物化学已成为探索中药效应成分的有效方法，然而由于当时分析技术的局限，检测及表征体内成分的能力不足，它只考虑定性或定量的化学成分，并没有考虑到效应评价。只有在治疗有效性的前提下，将体内化学成分与中药疗效相关联，才能揭示中药的有效成分。因此，我们引入代谢组学建立新的研究方法来弥补中药血清药物化学在解决效应评价方面的不足。

代谢组学是系统生物学的重要组成部分，研究思路与中医药整体观不谋而合[24,25]，针对中药复杂性和效应整体性，综合考虑中药方剂体内化学成分的变化[26]，其特征与中医药的整体观念一致[27]，表明代谢组学可促进证候本质和方剂复杂作用机制解析。

“辨证论治，方证相应”是中医药治病基本原则。方剂疗效评价必须基于对证候的科学阐释。中医证候是一种功能状态，是机体对体内外各种环境变化和致病因素做出的反应，它的本质是由机体不平衡而引起的代谢网络变化，这些内源性代谢成分变化反映证候生物学表型[28]。

代谢组学技术通过对内源性小分子代谢物的非歧视性分析，获得反映机体功能状态的代谢指纹特征和代谢网络[29]。利用代谢组学技术可表征证候生物标志物，阐明证候生物学本质，为证候诊断和相关动物模型的建立提供科学依据。利用代谢轮廓、代谢指纹、生物标记物可建立既符合中医特征又适合中医药研究的药效生物评价系统。

3.2. 中药血清药物化学理论

中药血清药物化学主要用于中药物质基础分析。虽然中药成分复杂，但只有被血液吸收的成分才可能发挥治疗作用[30]。这些成分包括原型成分和代谢产物。该方法已经用于筛选口服给药后体内有效物质的研究。方剂在配伍环境下药物在体内表达相关活性及相互作用。当在不同方剂和病理条件下，相同的中药可以表达不同的药效物质。因此，利用中药血清药物化学方法研究中药物质基础应从临床配伍的有效方剂入手。检测血液中的化学成分是中药血清药物化学理论的关键研究部分。随着液相色谱/质谱（LC/MS）技术，特别是具有高分辨率质谱串联超高效液相色谱的快速发展，快速检测和鉴定体内成分的能力已大大提高。这促进了中药血清药物化学方法的进一步普及[31]。液相色谱和质谱的串联使用提供了用于鉴定血液中代谢组分的有效检测方法，可全面获得直接作用物质信息。然而该技术也可检测体内内源性物质成分，严重影响中药外源性成分鉴定。因此，应在LC/MS数据处理过程中引入新方法解决该问题。

目前质量缺陷过滤（MDF）技术用于提取同源组分[32]。它通过设置适当的质量范围和多个过滤参数来分析质谱数据，从而滤除大量内源性干扰。背景扣除是一种以空白样品作为参照过滤掉含药生物样品中相同离子的分析技术[33]。其他用于药物代谢的分析软件，如MetaboLynx[34]和UNIFI[35]（Waters Corporation，美国），与预测代谢途径分析相结合可实现数据自动提取和代谢物辅助鉴定。

3.3. 整合中药血清药物化学与代谢组学

在20世纪90年代早期，笔者提出并建立了从含有血清的口服制剂中发现体内直接作用物质的研究设计。然而，由于当时没能有效地解释中医证候生物标志物，因此尚未建立用于方剂功效的精准评价系统，还不能将体内成分与中药功效有效联系起来。21世纪初，证候生物标志物发现和体内成分分析同步完成，在方剂有效状态下，将方剂体内成分与证候生物标志物相关联确定潜在有效物质。以方剂为研究对象，利用代谢组学发现和鉴定证候/疾病生物标志物，建立方剂疗效评价体系，阐明方剂功效，分析治疗有效状态下体内直接作用物质，进而将其与证候生物标志物相关联，鉴定与生物标志物轨迹变化高度相关的组分，确定有效物质并解析作用机制，解决了一系列与中药有效性相关的科学问题。总之，

利用代谢组学技术揭示证候生物学机制，采用中药血清药物化学发现体内活性物质，在有效性评价前提下对体内成分和生物标志物进行相关分析，揭示与方剂功效有关的效应成分。

整合中药血清药物化学与代谢组学构建中医方证代谢组学研究策略，揭示中医药的科学价值[36]。2015年，爱思唯尔出版了*Chinmedomics* [37]。中医方证代谢组学受到广泛关注，成为评价中药疗效以确定其效应物质的有效策略[38]。为了确定方剂功效相关成分，采用皮尔逊相关法建立PCMS（代谢物与血清成分的相关性标记）方法模型，利用*r*系数显示化学成分与体内生物标志物之间的关联程度[39]。该模型用于分析证候生物标志物的动态变化，辨识体内直接作用物质，发现与临床疗效高度相关的关键成分[6,40]。由于中药多组分作用于生物标志物，应进一步建立关键组分的动态优化模型，筛选最优的多组分候选化合物。

3.4. 关键技术和注意事项

该研究成果突破了以往的活性导向分离等天然药物研究活性成分方法的局限，使药效物质基础的研究紧密结合证候及方剂，使发现的药效物质基础与临床疗效相关联，打破药效物质基础研究与临床疗效脱节的瓶颈，形成4项递进的创新性关键技术：①基于代谢组学的证候生物标记物发现技术；②基于证候生物标记物的方剂临床疗效评价技术；③基于中药血清药物化学的方剂体内显效成分鉴定技术；④血清中外源性方剂显效成分与内源性证候生物标记物关联度分析技术。中医方证代谢组学研究方法的开发将极大地促进广泛应用，如揭示药物作用机制、有效性和安全性[41–45]。

中医方证代谢组学应用于中医证候生物学实质、中药/方剂临床疗效评价、药效物质基础发现等领域，用以解决与中药有效性相关的上市药品有效性再评价，方剂配伍规律，基于临床经验的新药创制，中药质量标志物的发现及中药材、饮片、中成药的质量控制等科学技术问题。应用中医方证代谢组学作为技术手段必须满足以下条件：①证候的中医诊断必须准确，避免兼证；②证候相关动物模型制备必须采用学术界认可的制备方法；③方剂/中药的效应评价必须将证候要素、临床化学与证候标记物整合分析；④内源性及外源性体内成分分析必须采用无歧视的全成分分析，并利用高分辨液相质谱、液相-核磁、气相-质谱等联用设备；⑤内源性标记物与外源性方剂成分关联度分析必须多途径进行，并进行生物学验证。

4. 创新和优势

中医方证代谢组学反映了中药临床给药形式以及中医方证相应的特殊性。基于此，中医方证代谢组学阐明了体内有效物质。众所周知，同一中药在不同方剂中于体内表达不同的有效成分，因此必须以方剂为研究对象，阐明方剂有效性是发现药效物质基础的前提。该方法不同于直接分析体内组分和体外筛选生物活性物质的研究方法，它使用反向研究策略来揭示药效物质基础。首先，该方法探索了中医证候/疾病的生物学本质，建立中药疗效评价体系；基于方剂有效性，评价证候/疾病治疗的整体疗效，解析有效性作用机制，分析效应成分，并对体内成分和证候生物标志物动态变化进行相关性分析，关联成分进一步经生物学验证以确定药效物质基础。

与代谢组学技术相比，中医方证代谢组学不仅仅研究内源性代谢产物，更关注来源于方剂的药物成分及其代谢产物[46,47]。早期的中药血清药物化学研究中多数研究仅关注正常动物给药后的体内成分及其代谢变化，少数研究关注疾病动物模型 [48–51]，但尚未将成分和药物治疗作用相关联，忽视体内成分与证候标记物的关联性，未能表达有效状态下体内成分的显效形式，研究结果与中药临床用药实践脱节。以往对方剂的效应评价仅仅采用有效的药理学及病理学指标评价，难以体现对证候的综合整体效应，而方证代谢组学是将证候要素、临床化学及证候代谢标记物整合分析评价方剂的疗效[52,53]。天然产物研究的活性导向分离方法难以体现方剂配伍下药物吸收过程中的相互作用和人体对药物的作用，更不能体现多成分的协同作用，导致分离过程中活性成分丢失，难以获得方剂表达疗效的临床实践特征[51,54]。随着研究的不断深入以及方法学的不断完善，中医方证代谢组学必将在中医证候本质、中药药效评价及中药质量控制研究中发挥更大的科学价值，促进中医药现代化进程及国际化发展。

5. 中医方证代谢组学应用进展

目前，生命科学研究已进入“组学”时代。生物标记物为疾病精确诊断提供了科学依据[55–58]，而利用中医方证代谢组学可实现中药疗效的客观评价。研究表

明中医方证代谢组学在发现生物标记物及揭示效应机制等方面起到了重要作用[59]。利用中医方证代谢组学表征了阳黄证[60,61]、肾阳虚证[62,63]、肾阴虚证[64]、心气虚证[65]、湿热黄疸证[66]、失眠证[67]、肝郁脾虚证[68]等证候的生物标记物，阐明了相应方剂茵陈蒿汤[69]、六味地黄丸[70]、知柏地黄丸[71]、肾气丸[72]、温心方[34]、酸枣仁汤[73]、生脉散[74–76]、天芪降糖胶囊[77]、双黄连[78]及其他中药材[79,80]的药效物质基础及作用机制。

5.1. 茵陈蒿汤药效物质基础的发现

茵陈蒿汤是治疗湿热黄疸证的经典方剂。利用中医方证代谢组学开展了茵陈蒿汤治疗湿热黄疸证的有效性研究，进而发现并确定药效物质基础及潜在效应靶点[81]。表征了茵陈蒿汤的69个化学成分，鉴定了41个血中移行成分，发现了34个尿液生物标记物；利用PCMS技术将证候标记物与显效状态下的体内成分相关联，发现了与效应关联的药效物质（图2）。结合效应靶标预测技术发现了12个潜在治疗靶点。进一步阐明了有效物质与其关键靶途径之间的关系，为设计新型组合药物提供研究基础。

5.2. 筛选关黄柏活性化合物

中药成分的生物学活性评价是探索药效物质基础的有效手段[82]。最新研究[83]利用中医方证代谢组学开展关黄柏抑制前列腺癌的效应研究并探索其活性成分[83]（图3）。结果显示关黄柏可以抑制22RV1人前列腺癌细胞移植肿瘤的生长[图3（a）]。利用中医方证代谢组学方法分析体内成分和代谢标记物，表征了关黄柏的54种化合物，发现了体内38个化合物[图3（c）]。辨识并鉴定了血清中29个原型化合物和9个代谢物，发现了34个生物标志物与前列腺癌相关；关黄柏可将代谢标记物调整到正常水平，将代谢轮廓调节至健康状态[图3（b）]，分析发现了10个入血成分与整体效应高度相关[图3（d）]。

5.3. 中医方证代谢组学发现开心散质量标记物

基于中药质量标志物研究建立质量标准以揭示其有效性和安全性[84,85]。开心散是用于治疗阿尔茨海默病（AD）的经典方剂。针对其质量标志物仍不清楚的问题，采用中医方证代谢组学技术探索开心散治疗转基因AD小鼠的有效性和潜在质量标志物[86]。研究发现开心散可以减少脑组织Aβ1-42的沉积，并显著地改善认知功能。分析体内生物标记物和化学成分，研究显示开心散通过调节20个生物标记物重新平衡脂质和氨基酸代谢异常。根据开心散对AD的疗效，确定了人参皂苷F1、人参皂苷Rf、去氢茯苓酸、20-*O*-吡喃葡萄糖基人参皂苷Rf、(*E*)-3,4,5-三甲氧基肉桂酸为开心散的质量标志物。

6. 未来展望

中医方证代谢组学促进了中药有效物质的发现并阐明了其作用方式，为阐释方证相应关系提供了一种新方

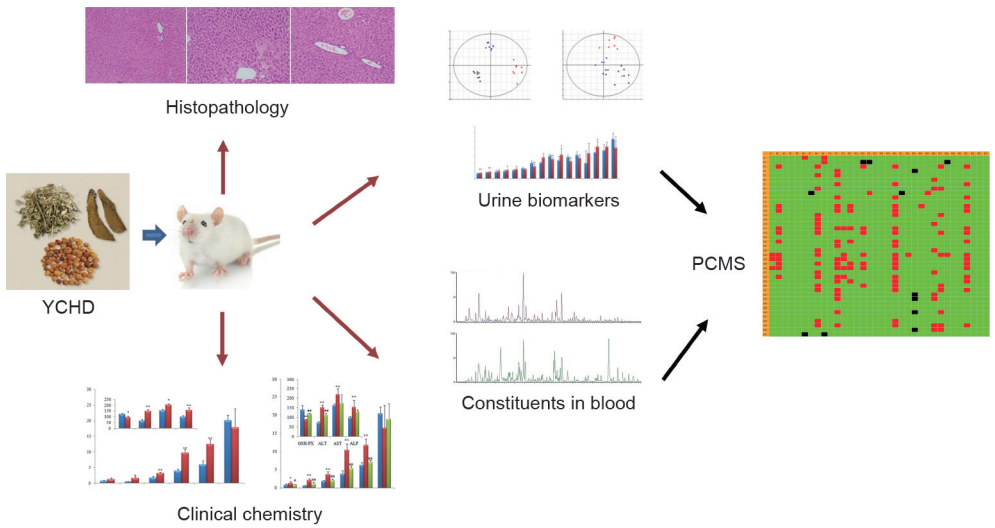

图2. 中医方证代谢组学促进茵陈蒿汤药效物质的发现。

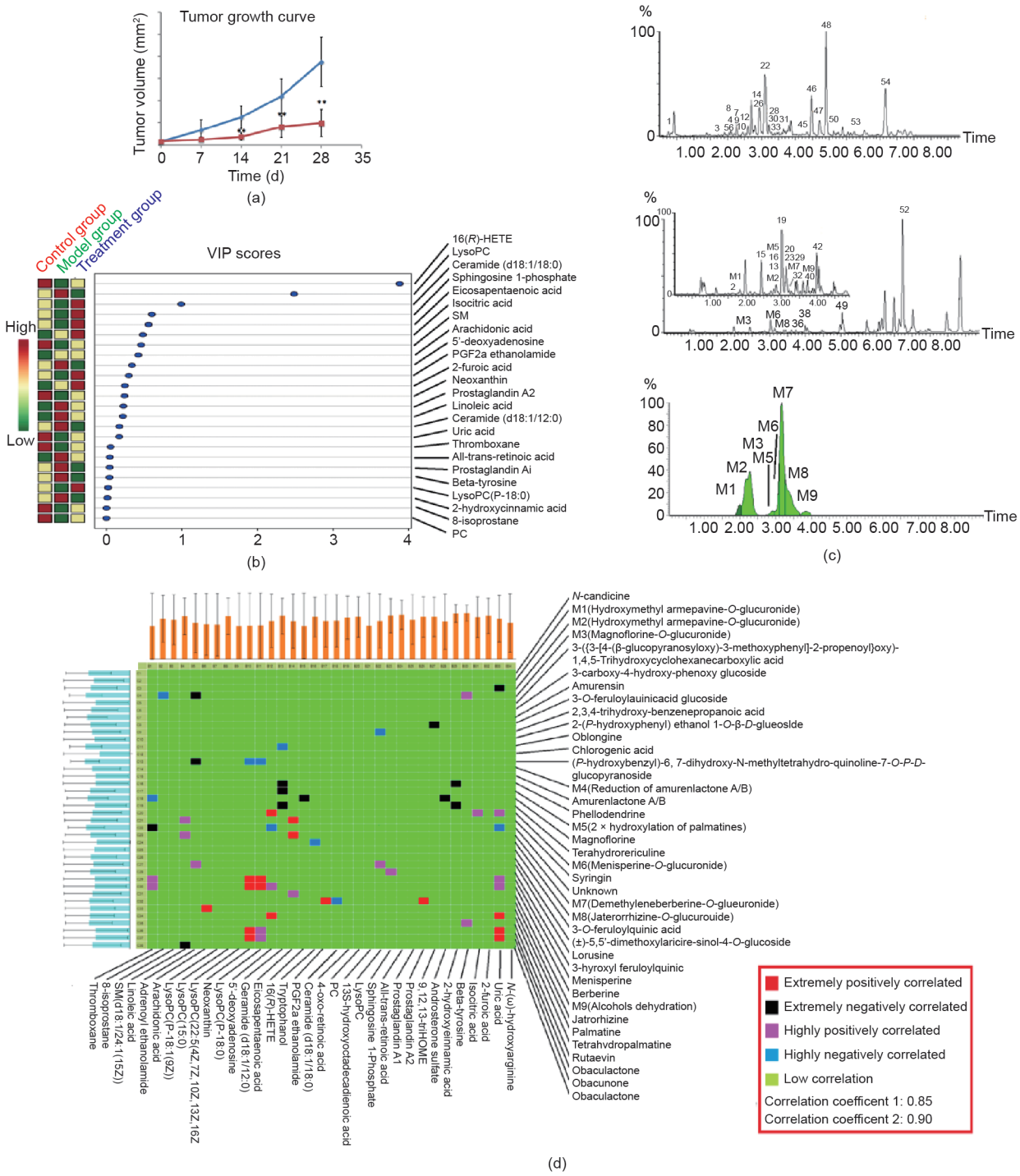

图3. 高通量中医方证代谢组学方法用于筛选关黄柏中的活性化合物。（a）模型组和治疗组肿瘤生长比较；（b）代谢组学生物标志物分析；（c）利用血清药物化学进行体内成分分析；（d）采用PCMS技术确定与效应高度关联的有效成分。

法。越早整合最新的先进技术越能提高先导化合物选择和优化的成功率，并有助于解释方剂治疗机制[87]。然而，由于证候的复杂性，仅在代谢物层面进行作用机制研究仍不足以全面反映生命活动本质，在代谢标记物研究基础上关注上游功能蛋白和基因，从而使证候生物学本质研究更深入、更具体，促使治疗更精准。这样将使方剂有效性评价和药效物质基础研究更具临床应用价值。

在中医方证代谢组学理论建立之初，我们已经考虑到此问题，研究实践中也在紧紧地与蛋白组学等其他组学相结合。由于代谢组学是该理论的核心技术，所以该理论中名为“中医方证代谢组学”，是以组学“omics”

进行定义的，也是考虑给该理论留出空间，在未来引入并整合蛋白组学、转录组学及基因组学等理论和技术，使该理论不断在实践中得以完善。同时，下一步将在各种临床常见证候患者大样本方证代谢组学分析、病证结合患者大样本方证代谢组学分析的基础上，通过大数据整合分析，建立涵盖常见中医证候及病证结合表型的代谢轮廓及生物标记物、代谢轮廓与有效方剂、生物标记物与有效成分的软件包，实现病证的精准诊断，在基于标记物分析的精准治疗和有效物质发现方面作进一步创新。

中医方证代谢组学提供了一种探索中医治疗效应的整合研究方法[88]。从生命科学的角度来看，它考虑整体动物、器官组织和细胞层面的基因、蛋白和代谢网络的整合变化，以便整体解析疾病病理机制。目前医学科学呈现出中医和现代医学和而不同的发展趋势[89–91]，我们应抓住科学和技术革命的重大发展机遇，中西医学界共同肩负逐步突破理念障碍，实现医学科学一体化的大健康目标。

7. 结论

精准医学必将在21世纪发挥重要作用。鉴于世界各国都非常重视中医药发展的国际现状，中国必须抓住机遇，满足临床需求，尊重中医原创思维，汲取精准医学理念，整合多学科知识，建立准确诊断和精确疗效评价技术平台，提高中医的临床疗效，为中医学和现代医学科学提供有效的交流和沟通方式。中医方证代谢组学是大数据时代精准医学的重要组成部分，已被广泛用于中医证候的精确诊断和方剂效应评价。中医方证代谢组学以精准生物标记物为桥梁，关联体内成分建立效应评价体系，揭示经典方剂和证候对应关系，这有助于实现中国式的精准医学模式。我们希望大力发展中医方证代谢组学平台，促进中医基础研究与临床资源的深度融合，进一步增强中医药研发的原始创新能力。

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Compliance with ethics guidelines

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