

· 学术探讨 ·

“中药嗅药”——一种中药应用的新形式

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[摘要] “中药嗅药”作为融合传统芳香疗法与现代鼻用递药技术的创新形式,承载中医“气香走窜、通窍醒神”的理论精髓。该文基于古籍中嗅药在急救、神志、肺系、妇科等病证中的系统记载,梳理其临床应用的历史演变,阐明“中药嗅药”作为新形式提出的深厚历史依据与理论可行性。结合现代中药嗅药在神经、呼吸、心血管等疾病中的剂型创新与精准应用,进一步从嗅觉受体通路、嗅脑通路、鼻黏膜血管与淋巴通道等多维路径加以解析,论证其快速起效、全身调节等优势。在中药外治需求持续增长、鼻用剂型技术不断突破、递药路径日益精准的背景下,中药嗅药展现出显著的现实适用性与发展潜力,旨在为该形式的系统构建提供理论支撑与实践方向。

[关键词] 中药嗅药; 芳香外治; 多通路机制; 靶向高效化

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"Olfactory Administration of Chinese Medicine"——A New Form of Application of Chinese Medicine

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[Abstract] As an innovative form of combining traditional aromatherapy with modern nasal medicine delivery technology, "olfactory administration of Chinese medicine" carries the theoretical essence of traditional Chinese medicine (TCM), which is "moving and channeling Qi and fragrance, dredging and awakening the mind". Based on the systematic records of olfactory therapies in ancient books in emergency care, disorders of consciousness, lung system, and gynecological diseases, this paper examines the historical evolution of its clinical application, and elucidates the profound historical basis and theoretical feasibility of "olfactory administration of Chinese medicine" as a new form. Combined with the innovation and precise application of modern Chinese medicine olfactory agents in multi-system diseases such as nervous, respiratory, and cardiovascular diseases, this paper further analyzes the multi-dimensional mechanism of olfactory receptor pathway, olfactory brain pathway, nasal mucosal blood vessels, and lymphatic channels, and demonstrates its advantages of rapid onset, targeted brain entry, and systemic regulation. Under the background of continuous growth in the demand for external TCM treatment, continuous breakthroughs in the technology of nasal dosage forms, and increasingly accurate drug delivery paths, Chinese medicine olfactory agents have shown significant practical applicability and development potential. This study aims to provide theoretical support and practical direction for the system construction of this form.

[Keywords] olfactory administration of Chinese medicine; aromatic external treatment; multi-pathway mechanism; targeted and efficient delivery

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中药作为中华医学瑰宝历经数千年积淀形成独特体系,然而传统用药形式如生药、饮片虽存药性本源却受限于剂型繁琐与药效波动,难符现代精准医疗需求。2001年国家推行中药配方颗粒实现标准化剂量与便捷服用^[1-3],但仍面临脂溶性/挥发性成分提取不足、口服安全性控制难及患者依从性差三大瓶颈^[4-6],驱动新型给药路径探索。中药外治自古依托“外治内应”“气香走窜”理论,以贴敷、熏洗等形式规避胃肠首过效应、实现靶向速效^[7-8],然传统粗制剂(膏药、洗剂等)存在成分失稳、渗透不足及剂量模糊等缺陷^[9]。本团队据此于2018年首创“配方精油”概念^[5,10-11],基于“芳香开窍”理论聚焦中药脂溶性成分优势,开发微剂量、多途径吸收的精准外治载体^[12];进而提出“中药吸嗅学”与“吸嗅疗法”理论^[13-14],界定了中药吸嗅学的内涵与外延,并凝练核心应用形式——“中药嗅药”。该应用形式的提出推动中药外治从经验性用药向机制驱动型精准干预的改变。本文首次系统构建中药嗅药理论体系,以期与中药现代化与创新外治技术的发展提供新的研究路径。

1 中药嗅药的定义与内涵

中药嗅药,是指来源于自然界、具备纯天然、挥发性、芳香性、脂溶性、小分子、气味可识别性等特征,经吸嗅途径(包括鼻腔吸入、黏膜吸收、嗅觉刺激入脑或作用全身)发挥药效的一种用药新形式^[14]。其药效物质基础以倍半萜类、芳香醛酮类、醚类、脂类、挥发性生物碱等为核心,基于“吸嗅适应性”功能分类体系,中药嗅药逐渐形成辟秽防疫^[15]、醒脑开窍^[16]、调节情志^[17]、通鼻宣肺^[18-19]、调经行气^[20]、温通心阳^[21]等相对独立的应用方向。作为继生药、饮片、配方颗粒、配方精油后的剂型演进产物(增强出版附加材料),其以起效快、靶向准、剂量可控、依从性高、文化属性强等特点,奠定该新形式的物质基础与分类学依据。

2 中药嗅药的理论基础

中药嗅药融合中医药传统理论与现代鼻用递药科学,是“中药”与“吸嗅”两个研究核心的有机结合体。尽管古代未以“嗅药”之名系统提出,但其深植“鼻为肺窍”“香药开窍”“脑为元神之府”经典理论,构建“从鼻入脑-以香行气-以气通神”完整干预链。古代医家强调“药气从鼻直达肺,通经贯络,透彻周身,卒病治病,从症用之,以助服药之所不及。”现代科学印证其主要通过嗅脑通路绕过血脑屏障、经三叉神经调节自主神经、由鼻黏膜血循环避免首过效应等多重机制,实现传统理论与现代递药科学的融合,为新型用药形式的建立提供理论可行性基础。

3 中药嗅药的古代文献应用

古籍溯源证实中药嗅药在古代临床应用广泛,其药性多温辛行散,具行气活血、通窍止痛、化湿辟秽、调神安志之功^[22-23]。施用方式涵盖“熏”(熏香、熏蒸、药熏房),“焚”(焚香、烧香、焚灸),“佩”(香囊、香袋、香佩),“闻”(嗅香、闻香、吸香、吹鼻、滴鼻、塞鼻),“涂”(点鼻、塞鼻、擦鼻翼)^[24-25]。中药嗅药既可用于急救及应急治疗,也广泛应用于神志、肺系、妇科、疫病及杂病等多类病证^[26-27]。

3.1 急救类 中药嗅药最早系统应用于急救领域。远古至

秦汉时期,主要以熏烟疗法(燃烧艾叶、菖蒲等)刺激鼻腔,以促醒“卒死”“尸厥”患者,但尚无明确剂型剂量记载;东汉《金匱要略》首创“薤汁灌鼻”液体鼻腔给药法^[28],标志着嗅药疗法从外部刺激到直接用药的变化;隋唐至明清时期,经鼻急救则发展出散剂吹鼻的主流形式,如通关散(半夏、细辛、皂角、薄荷等分)取“少许”(约豆大)药末吹鼻,通过激醒昏迷者,可达“得嚏则生”“立苏”的疗效^[29-30]。

3.2 神志类 东晋《肘后备急方》首载嗅药调神三法,包括佩香囊(菖蒲、藜芦等作散带之)、枕香具(犀角枕、青木香填充)、焚香熏衣(沉香等),用于治疗“卒魔寐不寤”等神志病症^[31];唐宋时期理论升华,《千金要方》提出芳香药具有“开窍调神之君”之功,《和剂局方》则推动芳香开窍类方药进入广泛临床应用阶段^[32];明代《普济方》载31首香方,创香薰、香包、香身诸法,实现了由“外助怡情”向“经鼻入脑、醒神开窍”认知模式的转变^[33-34];清代《理渝骈文》系统归纳熏、涂、吹、滴、塞、嗅六法,并结合药性与病机施治,奠基了中药嗅药调养外治体系的理论与实践基础^[35]。

3.3 肺系类 隋唐时期《千金要方》载吹鼻法(乱发灰“枣核大”)、塞鼻法(通草细辛末“豆大”)治鼻衄鼻窒^[36],《肘后方》以麻黄杏仁蒸气熏鼻缓喘^[31],体现“上窍通而肺气降”的治疗逻辑;宋以后迎来剂型革新,《太平圣惠方》以“细如轻尘”的龙骨散吹鼻,立止鼻血;三五滴辛夷-白芷麻油剂滴鼻,实现“清涕自收”;至明代,《本草纲目》记载22味熏吸药物及配伍应用,《医学正传》更首创治嗽烟筒方^[24],开创定量吸入装置先河。

3.4 妇科类 唐代《千金要方》已有半夏丸(“大豆大”)塞鼻通乳化痈的案例;《外台秘要》^[37]用皂荚末置鼻引嚏,促“胞衣立出”,为产后急症的鼻用干预奠定基础。宋代《妇人大全良方》以半夏末“少许吹鼻”助胎盘排出;并用“搐鼻香”散剂吹鼻治宫寒带下,记有“带下十日内止”的精准疗效。清代王孟英在《月经解》中进一步拓展吸入疗法,采用烧红铁秤锤淬醋生雾,令产妇吸入以防血晕,开创了气体芳香产科应用先河。

3.5 疫病类 战国《五十二病方》首创艾熏室以驱避“疠气”,开环境消毒之先河^[14];晋代《肘后备急方》升级为三寸香囊(薰草、雄黄)佩身,形成“秽气不染”个体防护模式;明代实现剂型与机制双突破,《温疫萃言》载孩儿菊叶塞鼻阻断疫气,《医方考》提出“疫从鼻入”理论,创雄黄塞鼻、大蒜泥丸填窍等方法,并载“男左女右”性别差异化给药原则;清代《慈禧光绪医方选议》^[38]集前代经验之大成,创“避瘟丹”(甘草、苍术等配枣泥“半斤”制饼),配合炭熏药烟,达成“解毒燥湿、祛瘟除邪”作用的立体防护体系。

3.6 杂病类 汉代《华佗神方》创“热蒸汽吸嗅法”止阴寒呃逆,取乳香、硫黄、陈艾等分酒煎,患者俯嗅药汽“寒呃立止”^[13];唐代《千金要方》定“小豆、瓜蒂、糯米散”极细末鹅羽轻吹,治小儿伤寒发黄,“黄退目清,三日瘥”;明代《本草纲目》^[37]则汇集多种鼻用与熏吸剂型,如皂角麝香散吹鼻治中风口噤,佩兰槟榔卷塞鼻防瘴,吴茱萸和木瓜汤熏吸治霍乱转筋,薄荷-冰片-硼砂散吹鼻愈咽痛等,且剂量精准至吹鼻“方寸匕”、塞鼻“梧子大”、熏蒸“汤一斗三刻”。

综上,中药嗅药虽无古名,但大量的古籍考证证实中药

嗅药已形成“嗅入达脑,气达病所”体系化实践,为新用药形式的提出奠定历史必然性依据。

4 中药嗅药的现代精准化应用

现代中药嗅药已逐步建立精准递送剂型体系,涵盖滴鼻油^[39]、鼻喷剂^[40]、单味/复方精油^[41-42]、干粉吸入剂^[43]、雾化剂^[44]、温敏鼻凝胶^[45]等多种形式,同时,精油辅以电热挥发器、喷雾器、香薰灯、扩香器、加湿器等扩散设备使用^[13]。其核心突破在于将脂质体、纳米粒、外泌体等靶向载体引入精油制剂^[46],显著提升药物成分稳定性、鼻黏膜穿透力与靶向效率,从而实现生物利用度优化与剂量精准控制,并在多系统疾病治疗中展现出良好疗效^[17-18,21,47-48]。

4.1 神经系统疾病 神经系统疾病治疗中,中药嗅药可实现精准干预。醒脑静鼻腔喷雾剂(麝香、栀子、郁金等组成),以毫升级给药剂量,能迅速改善卒中后吞咽障碍^[49];冰麝液(30 mL+10 mL蒸馏水)结合 $4\text{ L}\cdot\text{min}^{-1}$ 氧气经鼻导管吸入30~45 min,具活血通络、开窍醒神之功^[50];菖参花精油滴鼻5~10 $\mu\text{L}/\text{次}$, (2次/d \times 21 d),可提升神经可塑性,缓解大鼠抑郁行为^[41];雷公藤多苷脂质体(0.425~1.70 $\text{mg}\cdot\text{kg}^{-1}$, 40 $\mu\text{L}/\text{d}\times$ 21 d)经鼻给药,可显著改善中枢炎症模型小鼠的认知障碍^[51];延胡索乙素溶液以3 $\text{mg}\cdot\text{kg}^{-1}$ 鼻腔给药,可抑制偏头痛模型动物脑内内皮素和5-羟色胺水平,改善神经痛症状^[52]。

4.2 呼吸系统疾病 呼吸系统疾病中,中药嗅药在黏膜修复与抗炎抗过敏方面展现出明确优势。苍夷滴鼻油可促进鼻黏膜损伤修复^[53];薰衣草精油吸入可促进纤毛运动、缓解支气管痉挛,改善哮喘症状^[54];辛夷挥发油纳米脂质体滴鼻剂(5.01 $\text{g}\cdot\text{L}^{-1}$)早晚1滴治疗儿童变应性鼻炎效果显著^[55];鼻鼾通窍方鼻喷剂(每侧1揆/d \times 2周),有效改善鼻炎患儿症状^[56];多种精油(薄荷、茶树、柠檬等)纳米乳雾化吸入则可显著减轻鼻炎症状,缓解炎性细胞浸润和黏膜水肿^[57]。

4.3 心血管系统疾病 心血管系统疾病中,中药嗅药主要通过调控循环相关因子与神经内分泌系统发挥作用。心绞痛滴鼻剂(2~3滴/次)可缓解冠心病心绞痛症状^[58];心安宁滴鼻剂(2喷/孔,含药量约2.4 $\text{g}\times$ 3次/d \times 4周)对不稳定型心绞痛起效迅速^[59];薰衣草精油吸入30 min可降低血浆肾素活性(PRA)、血管紧张素 I (Ang I)、血管紧张素 II (Ang II)与醛固酮(ALD)等血压相关因子水平^[60];柠檬香脂精油吸入10 min可通过调节皮质酮改善循环系统自主调控功能^[61]。

4.4 妇科及其他疾病 妇科及其他领域中,中药嗅药也显示出广泛应用潜力。柠檬精油湿敷纱布嗅闻30 min可有效降低腹腔镜术后24 h内恶心呕吐发生率^[62];复方芳香棒(薰衣草、薄荷、橙花等)术后吸嗅可缓解恶心不适^[63];于月经前3 d起吸嗅薰衣草精油30 $\text{min}\cdot\text{d}^{-1}$,连续2个周期,可显著降低痛经疼痛评分^[64]。综上,现代嗅药以精准剂量与明确剂型实现多系统疾病干预,奠定了新形式应用的现实基础。

5 中药嗅药的现代多通路作用机制

中药嗅药建立“局部识别-中枢调控-全身分布”三位一体机制,多通路机制研究为新形式提供实验科学依据。中药嗅药的多通路作用机制见增强出版附加材料。

5.1 嗅觉受体通路 中药嗅药经嗅觉受体通路实现气味的

别:芳香分子激活嗅上皮中的嗅觉受体(ORs),该受体属于G蛋白耦联受体(GPCR)家族,继而耦联嗅觉型鸟苷酸结合(G_{olf})蛋白,激活腺苷酸环化酶生成环磷酸腺苷(cAMP),进一步开启钠/钙通道触发动作电位^[65]。周炜炜等^[66]证实辛香类中药(陈皮、丁香、小茴香)挥发油成分可通过激活特定OR,触发相应信号通路,从而产生辛香气味效应,为“辛味药性”的物质基础与分子机制提供了重要依据。

5.2 异位嗅觉受体通路 嗅觉受体亦广泛分布于多种非嗅觉组织(皮肤、脑组织、肝、肺、心、肠、睾丸、脂肪组织等),这些受体被称为异位ORs^[67-68]。与ORs不同的是,异位ORs并不直接参与嗅觉与神经感觉过程,而是通过配体-受体结合调控细胞内信号传导来发挥相应的生物学效应。有研究发现薰衣草醇/薄荷脑吸入后可激活肺部气道平滑肌细胞中的嗅觉受体家族2亚家族W成员3(OR2W3)、嗅觉受体家族2亚家族AG成员1(OR2AG1)异位嗅觉受体,进而调节钙离子(Ca^{2+})浓度,诱导钙调蛋白依赖性蛋白激酶激酶 β (CaMKK β)-腺苷酸活化蛋白激酶(AMPK)磷酸化级联反应,实现支气管舒张、纤毛运动增强及抗炎效应^[69-70]。该机制为中药挥发成分(如辛夷油、艾叶酮)靶向呼吸道疾病提供新的潜在干预路径。

5.3 嗅脑通路 嗅脑通路是中药挥发性成分实现中枢靶向作用的核心路径:芳香小分子结合嗅上皮G蛋白耦联受体(GPCR),激活G蛋白信号,继而触发电信号经嗅神经穿筛板入嗅球,并进一步投射至边缘系统(杏仁核/海马体/嗅皮层)等脑区^[71-74]。该通路可规避血脑屏障与首过效应,实现约5~10 s级超快入脑,为冰片促醒^[50]、菖参花精油抗抑郁^[41]、雷公藤多苷脂质体改善认知^[51]等嗅药中枢效应提供了关键递送通道。

5.4 三叉神经通路 三叉神经通路介导中药嗅药的持久生理调控:药物首先激活鼻黏膜三叉神经眼支(V1)/上颌支(V2)分支瞬时受体电位香草素亚型1(TRPV1)/瞬时受体电位锚蛋白1(TRPA1)通道,触发动作电位产生,信号继而经三叉神经节传至脑干感觉核与脊束核^[75-77],并进一步上行投射至下丘脑(下丘脑-垂体-肾上腺(HPA)轴调节)、蓝斑核(去甲肾上腺素释放)、延髓(自主神经控制)^[78-79]。该通路有分钟级延迟但持续数小时的作用特征,为延胡索乙素缓解三叉神经痛^[52]、薄荷精油止头痛、冰片促觉醒等提供长效干预基础^[78,80]。

5.5 鼻黏膜-血循环通路 鼻黏膜-血循环通路可实现中药嗅药全身快速递送:鼻中隔及下鼻甲区富含多孔毛细血管网,药物经细胞旁路及跨细胞转运在5~8 min内吸收入血,直入颈静脉-心循环系统,从而规避肝脏首过效应,其生物利用度达口服给药的3~5倍。该路径使心安宁滴鼻剂治疗心绞痛^[59]、薰衣草精油在降压、调经等方面的潜在效应得以实现^[60,64],使相关活性成分快速分布至心肺、内分泌、生殖系统等靶器官,发挥抗炎、改善微循环及激素调节等全身性药理作用。

5.6 鼻脑淋巴通路 鼻脑淋巴通路介导中药嗅药的中枢-外周免疫调节:药物可经嗅神经周围间隙进入脑膜下腔及鼻相关淋巴组织(NALT),并通过糖胶聚糖通道实现脑脊液-间质液双向交换^[81]。该路径使嗅药成分被NALT树突细胞捕获并激活局部免疫反应;或沿嗅神经通道进入颅底淋巴系统,

从而调节全身免疫,并在一定程度上延缓神经退行性病变进程^[82-83]。

5.7 肺吸收通路 肺吸收通路可实现中药挥发性成分的深度系统递送。粒径约1~5 μm的微粒经鼻吸入后沉积肺泡,并经I/II型肺泡上皮细胞10~15 s快速跨膜,进入肺循环系统,实现全身分布,同时有效规避肝脏首过效应^[17]。该路径可使辛夷挥发油纳米脂质体滴鼻剂^[55]、复方精油雾化剂^[57]等成分约5 min内直达支气管及肺泡靶区,从而显著提高生物利用度,不仅为鼻炎提供快速干预基础,还同步产生抗炎与免疫调节等全身性作用。

6 讨论

6.1 中药嗅药作为用药新形式的可行性和现实性 中药嗅药从传统经验性外治逐步迈向现代精准化靶向递送,充分体现其作为新型给药途径的可行性与现实性。而这一转变的核心驱动力是临床需求的不断提升。古代受限于提取工艺与载体形式,嗅药多以艾叶、菖蒲、麝香等芳香生药粗加工后经熏烟、吹鼻、塞鼻等方式使用。因有效成分含量低、作用轻且持续时间短,其疗效主要依赖“芳香走窜、开窍醒神”的整体宣通或急救刺激,缺乏精准性与靶向性。随着现代制剂技术发展,嗅药逐渐演进为以精油为核心的鼻用喷雾剂、气雾剂、凝胶、脂质体、纳米粒等多级智能递药系统,具有“用量小、起效快、作用强”的优势,可快速透过鼻黏膜,精准作用于中枢、呼吸、心血管及循环等系统,有效增强药效并延长作用时间^[13]。前期团队的大量实验研究亦充分验证了中药嗅药的可行性与应用潜力^[41-42, 47-48, 84],为临床推广与作用机制研究奠定了基础。与此同时,给药方式已由粗放应用,升级为定量喷雾、控释和靶向递送;剂量控制由“少许”“适量”发展为基于药动-药效学的微升级精准给药;疗效评价也由经验观察转向炎症因子水平、认知评分及生物标志物等客观量化体系。由此,中药嗅药已实现从低效广谱的传统经验手段,到向高效精准的中枢递送与系统调控策略的跨越式发展,为中药外治的现代化与国际化发展提供了坚实支撑。

6.2 中药嗅药作为用药新形式面临的挑战 当前,“中药嗅药”应用新形式的落地仍面临3重挑战:①理论标准化不足,芳香类中药成分复杂、成分间协同或拮抗关系尚不明确,根本症结在于传统经验表达与现代机制研究之间仍存在脱节。更为关键的是,当前嗅觉受体等分子信号机制虽已初步探明,但尚未将特定香气分子与具体药效作用形成系统性对应,缺乏“从气味识别到治疗靶点”的完整链条。②剂型发展不充分,当前上市鼻用制剂多局限于鼻腔局部疾病治疗(如鼻炎、黏膜修复)^[85],面向中枢疾病及全身性疾病的靶向制剂尤为匮乏,传统滴鼻液仍占主导地位,且普遍存在黏膜滞留差、剂量波动大等缺陷,导致其技术附加值低、市场竞争力偏弱;③成药应用亟待加强,尽管中药嗅药在多系统疾病干预方面展现出巨大潜力,相较于西药与生物药在鼻喷疫苗^[86-87]、抗病毒喷雾剂^[88]等重大领域取得的成功,中药嗅药的转化进程仍相对滞后。这主要源于“病-药-剂型适配逻辑不清”“有效成分递送效率低下”等关键机制研究的相对匮乏,导致其干预潜力尚未完全释放为成熟的、可广泛应用的

创新制剂产品。

6.3 中药嗅药作为用药新形式的突破路径 突破路径在于:①以课题组已构建的“中药嗅药的特点及应用数据库”为基础,系统解析中药芳香成分与其通路靶点的关联,建立“成分-受体-通路-效应”多维网络模型;结合钙成像、光纤记录等前沿技术,量化不同嗅觉模式的中枢响应规律,为传统“芳香通窍”理论构建分子层级的量效关联模型,推动中药嗅药理论向机制明确、指标可控、评价统一的现代体系升级,破解“理论标准化不足”难题。②锚定脑部及全身重大疾病需求,协同推进药材标准化-活性成分筛选-剂型创新-临床验证全链条研发。重点突破脑靶向递送瓶颈,筛选麝香酮、冰片等具有“通窍入脑”传统的精油活性成分^[89],设计脂质体/纳米粒包裹的喷雾系统^[90],显著提升嗅黏膜滞留性与血脑屏障穿透效率,构建“临床疗效导向”的产学研转化链,突破“剂型发展不充分”与“成药转化弱”的共性壁垒。③通过将中药嗅药纳入《中华人民共和国药典》吸入制剂指导原则,制定中药嗅药制剂技术规范,加速重大品种转化(如藿香正气鼻喷疫苗),以标杆产品验证技术路径,最终建立以“中国香气”为标识的全球标准体系,引领中药外治智慧的国际认可与应用。

6.4 中药嗅药作为用药新形式的前景展望 通过上述路径,中药嗅药将依托脑科学突破与精准递送技术,率先在脑病领域实现临床补充,并逐步拓展至全身性疾病防控;其“鼻腔-脑”靶向优势与绿色纯天然属性,高度契合中药新质生产力对高效、精准、可持续的核心要求。未来,以标准体系为支撑、以重大品种为载体的中药嗅用制剂,有望成为服务全生命周期健康管理的全球化中药创新名片。

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