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Specialty Committee of Research on Safety of Clinical Usage of Drugs of WFCMS

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雷公藤多苷片治疗慢性肾脏病合理用药指南

Guidelines for Rational Use of Tripterygium Wilfordii Polyglycosides Tablet in the Treatment of Chronic Kidney Disease

（草案，以最终出版稿为准）

世界中联分支机构标准
Committee Standard of WFCMS

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前　言

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主要起草单位：深圳市中医院、中日友好医院、河南中医药大学第一附属医院、北京中医药大学、北京市和平里医院、深圳市人民医院。

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本文件的起草程序遵守了世界中医药学会联合会发布的 SCM1.1-2021《标准化工作导则第 1 部分：标准制修订与发布》。

引　言

慢性肾脏病（chronic kidney disease， CKD）患病率逐年升高，已成为全球性的公共卫生问题。自 1981 年黎磊石教授等首开雷公藤提取物治疗肾小球肾炎的先河以来，雷公藤多苷片已被广泛应用于治疗慢性肾小球肾炎、IgA 肾病（Immunoglobulin A Nephropathy，免疫球蛋白 A 肾病）、狼疮性肾炎、紫癜性肾炎、糖尿病肾脏疾病等多种慢性肾脏疾病，在降低尿蛋白、保护肾功能等方面有着显著疗效。其作用机制主要包括：通过抑制核因子κB（nuclear factor kappa-B，NF-κB）等信号通路，降低肿瘤坏死因子α（tumor necrosis factor α，TNF-α）、白介素 6（interleukin 6，IL-6）等炎症因子表达，减轻肾脏局部炎症反应；调节 T 淋巴细胞亚群比例及 B 淋巴细胞功能，抑制免疫复合物沉积；上调足细胞关键蛋白，如 Nephrin、Podocin 等的表达，稳定细胞骨架，从而降低蛋白尿、延缓肾小球硬化进程。与其他免疫抑制剂相比，雷公藤多苷片价格相对低廉，患者经济负担较小。该药被纳入 2018 年版《国家基本药物目录》、2020 年版《国家基本医疗保险、工伤保险和生育保险药品目录》甲类目录，并被中国多项慢性肾脏病相关指南纳入。雷公藤多苷片在肾脏病领域的实际临床应用在一定程度上已超出了说明书所规定的适应证范畴，有大量的临床研究结果作为佐证。在 CKD 蛋白尿的治疗中，雷公藤多苷片常与血管紧张素转换酶抑制剂（Angiotensin-Converting Enzyme Inhibitors，ACEIs）、血管紧张素受体拮抗剂（Angiotensin Receptor Blockers，ARBs）、糖皮质激素、钙调神经磷酸酶抑制剂等多种药物联用，但尚缺乏系统的研究报道雷公藤联合以上药物的获益与风险。此外，雷公藤多苷片具有肝、肾、血液和生殖等多系统毒性：在肾脏可诱导肾小管上皮细胞凋亡和间质炎症，引发急性肾损伤；在肝脏通过氧化应激损伤肝细胞，引发药物性肝炎；在血液系统可抑制骨髓造血功能，导致白细胞或血小板减少；在生殖系统干扰性激素合成及生殖细胞成熟，导致女性闭经、男性精子活力下降。值得注意的是，其肾损害常为可逆性，与马兜铃酸导致的慢性纤维化不同，但仍需密切监测。不规范使用可增加不良反应发生风险，尤其对于肝功能异常、有生育需求的育龄期患者等特殊人群，需要规范的指导。因此，雷公藤多苷片如何合理应用于 CKD 的治疗，与其他药物相比疗效和不良反应风险如何，是亟须解决的临床问题。

本文件从临床实际出发，开展雷公藤多苷片治疗 CKD 合理用药的循证研究，遵循“循证为举，共识为辅，经验为鉴”的原则，基于现有最佳证据，在广泛共识基础上形成雷公藤多苷片治疗 CKD 的推荐意见，以保证指南的科学性、实用性、临床可操作性，指导中医、西医临床医生规范化使用雷公藤多苷片治疗 CKD，指导药师开展药学服务做好患者教育，提高临床疗效，减少不良事件，提高患者生活质量，节约医疗卫生资源。

雷公藤多苷片治疗慢性肾脏病合理用药指南

1 范围

本文件规定了临床应用雷公藤多苷片治疗慢性肾脏病的用药前评估、适应证、疗效评估、用药禁忌、药物相互作用、用药注意事项及不良反应等内容。

本文件适用于指导临床医生、药师合理使用雷公藤多苷片治疗慢性肾脏病。

2 规范性引用文件

下列文件中的内容通过文中的规范性引用而构成本文件必不可少的条款。其中，注日期的引用文件，仅该日期对应的版本适用于本文件；不注日期的引用文件，其最新版本（包括所有的修改单）适用于本文件。

国际疾病分类第十一次修订本（ICD-11）

3 术语和定义

下列术语和定义适用于本文件。

3.1

雷公藤多苷/雷公藤多甙

由卫矛科植物雷公藤（*Tripteryqium wilfordii* Hook. f.）的干燥根及根茎中提取纯化精制而成的极性较大的脂溶性混合物。

注：主要活性成分有二萜类、三萜类、生物碱类等。

3.2

雷公藤多苷片

由雷公藤多苷制成的浅黄色至棕黄色片剂。

注：味微苦、涩。具有祛风解毒、除湿消肿、舒筋通络功效，有抗炎及抑制细胞免疫和体液免疫等作用，用于风湿热瘀、毒邪阻滞所致的类风湿关节炎、肾病综合症、白塞氏三联症、麻风反应、自身免疫性肝炎等。

3.3

慢性肾脏病

由多种原因引起的慢性肾脏结构和功能异常，且持续时间超过 3 个月。

3.4

肾病综合征

由各种原因导致的大量蛋白尿（≥3.5g/24h）、低白蛋白血症（＜30g/L）、水肿和（或）高脂血症。

4 概述

《延缓慢性肾脏病进展临床管理指南（2025 年版）》推荐，在患者可耐受的情况下尽量控制和减少尿蛋白水平，理想状态是直至在尿常规检查中转阴。中医中药在 CKD 的治疗中发挥了重要作用，其中雷公藤多苷片被认为是一种具有明确降低尿蛋白水平的中药单药提取物，临床应用广泛。

药理学研究表明雷公藤多苷片具有类免疫抑制剂作用，基础研究也逐渐揭示了其抑制肾小球系膜细胞及基质增生、改善肾小球滤过膜通性、减轻足细胞损伤等机制。

5 推荐意见及临床证据

5.1 慢性肾脏病患者，雷公藤多苷片联用 ACEI/ARB 与 ACEI/ARB 相比，哪个能使患者获益更多？

推荐意见：推荐雷公藤多苷片联合 ACEI/ARB，用于降低慢性肾脏病蛋白尿，效果优于单用 ACEI/ARB。（证据级别：极低；推荐强度：强推荐）

雷公藤多苷片联合 ACEI/ARB 有进一步降低血肌酐及尿素氮的作用，其机制可能与改善蛋白尿有关。（证据级别：极低；推荐强度：条件性推荐）

使用条件：适用于糖尿病肾病、慢性肾小球肾炎、IgA 肾病。

安全性：与 ACEI/ARB 相比，联用雷公藤多苷片后总体不良反应有所增加，主要表现为女性月经紊乱、闭经及男性阳痿、谷丙转氨酶/谷草转氨酶升高及白细胞减少、血小板减少。

证据描述：

共纳入 96 篇文献，88 篇研究结局报告了 24 小时尿蛋白，79 篇报告了血肌酐，36 篇报告了尿素氮。针对 24 小时尿蛋白的 Meta 分析结果显示：雷公藤多苷片联合 ACEI/ARB 与单用 ACEI/ARB 相比，可进一步降低 24 小时尿蛋白[MD=-0.55，95%CI（0.58，0.52），P＜0.001，I^2=99%，T/C：4725/4641，极低质量证据]。以慢性肾脏病类型进行亚组分析，结果显示对于糖尿病肾病、慢性肾小球肾炎、IgA 肾病，联合用药组降尿蛋白的疗效更优。针对血肌酐的 Meta 分析结果显示：与对照组相比，雷公藤多苷片联用 ACEI/ARB 可进一步降低血肌酐，[MD=-15.55，95%CI（-20.09，-11.01），P＜0.001，I^2=99.8%，T/C：4915/5086，极低质量证据]。针对尿素氮的 Meta 分析结果显示：与对照组相比，雷公藤多苷片联用 ACEI/ARB 可进一步降低尿素氮[MD=-1.04，95%CI（-1.89，-0.19），P=0.008，I^2=99.5%，T/C：1853/1802，极低质量证据]。

共 85 篇报道不良反应，其中随机对照研究 76 篇、队列研究 9 篇，Meta 分析结果显示：联合治疗组不良反应发生率 10.7%（368/3441），单用 ACEI/ARB 组 6.3%（202/3208），两组有统计学差异[RR=1.39，95%CI（1.14，1.71），P＜0.001，I^2=15.3%，低质量证据]。

亚组分析显示：联合治疗组生殖系统总不良反应发生率较高，8.89%（56/630）vs 0.35%（2/579），二者差异有统计学意义[RR=5.52，95%CI（2.03，15.04），P＜0.01，I^2=0%，极低质量证据]。联合治疗组肝功能异常发生率略增高，5.73%（134/2338）vs 1.10%（25/2273），二者差异有统计学意义[RR=1.52，95%CI（1.07，3.57），P＜0.001，I^2=0%，低质量证据]。联合治疗组血液系统的不良反应（白细胞减少、血小板减少、嗜酸性粒细胞增多）发生率增高，4.17%（82/1966）vs 1.44%（28/1937），二者差异有统计学意义[RR=3.57，95%CI（2.39，5.33），P＜0.001，I^2=21.8%，低质量证据]。

5.2 慢性肾脏病患者，单独使用雷公藤多苷片与 ACEI/ARB 相比，哪个能使患者获益更多？

推荐意见：可单独使用雷公藤多苷片治疗慢性肾脏病蛋白尿，其效果与 ACEI/ARB 相当。（证据级别：极低；推荐强度：条件性推荐）

雷公藤多苷片与 ACEI/ARB 均可轻度降低血肌酐、尿素氮，其机制可能与改善蛋白尿有关。（证据级别：极低；推荐强度：条件性推荐）

使用条件：存在 ACEI/ARB 禁忌症（高钾血症、双侧肾动脉狭窄等），或使用 ACEI/ARB 出现严重不良反应（低血压、干咳等）时，可优先选用雷公藤多苷片。

安全性：与 ACEI/ARB 相比，雷公藤多苷片不增加总不良反应，雷公藤多苷片的主要表现为女性月经紊乱、闭经及男性阳痿、谷丙转氨酶/谷草转氨酶升高及白细胞、血小板减少。

证据描述：

共纳入研究 16 篇，包括随机对照试验 15 篇，前瞻性队列研究 1 篇。13 篇研究结局报告了 24 小时尿蛋白，12 篇报告了血肌酐，11 篇报告了尿素氮。Meta 分析结果显示：单用雷公藤多苷片与单用 ACEI/ARB 相比，可进一步降低 24 小时尿蛋白定量[MD=-0.40，95%CI(-0.58，-0.21），P＜0.001，I^2=96%，T/C：508/492，极低质量证据]。单用雷公藤多苷片与单用 ACEI/ARB 相比，均有轻度降低血肌酐的趋势，[MD=-3.38，95%CI（-8.75，3.96），P=0.46，I^2=94%，T/C：468/460，极低质量证据]，均有轻度降低尿素氮的趋势[MD=-2.29，95%CI（-3.74，-0.84），P＜0.01，I^2=97%，T/C：222/218，极低质量证据]。

共 8 项研究报道不良反应，Meta 分析结果显示：雷公藤多苷片与 ACEI/ARB 相比，不良反应发生率略增高，雷公藤多苷组 12.1%（33/273），ACEI/ARB 组 11.0%（29/263），但两组无统计学差异[OR=1.09，95%CI（0.43，2.73），P=0.86，I^2=39%，极低质量证据]。亚组分析结果显示，单用雷公藤多苷片与单用 ACEI/ARB 相比，消化系统不良反应发生率升高（6.7% vs 0.0%），且二者有统计学差异[RR=4.60，95%CI（1.33，15.87），P=0.02，I^2=0%，T/C：195/183，极低质量证据]。

5.3 慢性肾脏病患者，单独使用雷公藤多苷片与激素相比，哪个能使患者获益更多？

推荐意见：在某些情况下，可单独使用雷公藤多苷片治疗慢性肾脏病蛋白尿，其效果优于糖皮质激素。（证据级别：极低；推荐强度：强推荐）

使用条件：糖尿病肾病、类固醇糖尿病等不适宜用激素的慢性肾脏病蛋白尿患者，或对激素不良反应（肥胖、白内障、股骨头坏死等）有顾虑的患者，激素抵抗者，可考虑优先使用雷公藤多苷片。

安全性：与激素相比，单独使用雷公藤多苷片总不良反应发生率较低。其中雷公藤多苷

片继发感染的比例低于糖皮质激素，而消化系统、血液系统、生殖系统、内分泌系统、皮肤不良反应发生率无差异。

证据描述：

共纳入 7 篇文献，均为随机对照试验，其中报道 24 小时尿蛋白 2 篇、血肌酐 3 篇、尿素氮 3 篇。Meta 分析结果显示：单用雷公藤多苷片与单用激素相比，有进一步降低 24 小时尿蛋白定量的趋势[MD=-0.95，95%CI（-1.88, -0.02），P=0.05，I^2=90%，T/C：291/270，极低质量证据]。单用雷公藤多苷片与单用激素相比，均有轻度降低血肌酐的趋势[MD=-12.99，95%CI（-31.94，5.96），P=0.18，I^2=37%，T/C：126/107，低质量证据]，均有轻度降低尿素氮的趋势[MD=-1.11，95%CI（-2.65，0.43），P=0.16，I^2=92%，T/C：126/107，低质量证据]。

共 6 篇研究报道不良反应，Meta 分析结果显示：雷公藤多苷组不良反应发生率较低 40.2%（117/291） VS 84.1%（227/270），两组存在统计学差异[RR=0.48，95%CI（0.38，0.61），P＜0.001，I^2=2%，低质量证据]。亚组分析显示单用雷公藤感染风险发生率较低（3.9% vs9.7%），二者差异存在统计学意义[RR=0.37，95%CI（0.14，0.97），P=0.04，I^2=0%，T/C：6/13，低质量证据]。

5.4 慢性肾脏病患者，雷公藤多苷片联用激素与单独使用激素相比，哪个能使患者获益更多？

推荐意见：可选择雷公藤多苷片联用激素治疗慢性肾脏病蛋白尿，其效果优于单用激素。（证据级别：极低；推荐强度：强推荐）

使用条件：适用于单用激素降蛋白尿效果不理想的患者。

安全性：与单用激素相比，未发现联合用药增加不良反应。

证据描述：

共纳入 62 篇文献，均为随机对照试验，其中报道 24 小时尿蛋白 48 篇、血肌酐 30 篇、尿素氮 18 篇。Meta 分析结果显示：雷公藤多苷片联用激素与单用激素相比，有进一步降低 24 小时尿蛋白定量的趋势[MD=-0.62，95%CI（-0.70，-0.55），P＜0.001，I^2=92%，T/C：1851/1846，低质量证据]。亚组分析显示，联合治疗组对不同程度的蛋白尿水平均有进一步降低效果。雷公藤多苷片联用激素与单用激素相比，有轻度降低血肌酐的趋势[MD=-9.92，95%CI（-13.27，-6.56），P＜0.001，I^2=91%，T/C：1051/1047，低质量证据]，有轻度降低尿素氮的趋势[MD=-0.79，95%CI（-1.03，-0.55），P＜0.001，I^2=71%，T/C：701/700，低质量证据]。

30 篇文献报道了不良反应，Meta 分析结果显示，联合治疗组不良反应发生率相对较低，联合治疗组 13.4%（155/1158），单用激素组 17.9%（203/1137），两组有统计学差异[RR=0.70，95%CI（0.43，1.14），P＜0.001，I^2=86%]。

5.5 慢性肾脏病患者，单独使用雷公藤多苷片与环磷酰胺相比，哪个能使患者获益更多？

推荐意见：在使用激素基础上，可选择雷公藤多苷片，降低蛋白尿的程度与环磷酰胺无差异。（证据级别：极低；推荐强度：条件性推荐）

使用条件：适用于单用激素降蛋白尿效果不理想的患者。

安全性：与环磷酰胺相比，雷公藤多苷片不增加总不良反应发生率，其不良反应主要包括肝功能异常、白细胞减少及胃肠道反应。

证据描述：

共纳入 8 篇文献，随机对照试验 6 篇，队列研究 2 篇，研究对象均为肾病综合征，所有研究均以激素作为基础治疗，雷公藤多苷片组的剂量均未超说明书规定剂量，环磷酰胺组的用药方法为常规推荐方法，研究疗程最短 1 个月，最长 18 个月。结局报道 24 小时尿蛋白 6 篇、血肌酐 2 篇。Meta 分析结果显示：雷公藤多苷片有进一步降低 24 小时尿蛋白定量的趋势，但无统计学差异[MD=-0.09，95%CI（-0.54，0.36），*P*=0.71，I^2=96%，T/C：207/199，极低质量证据]。雷公藤多苷片组改善血肌酐的作用略低于环磷酰胺，但无统计学差异[MD=0.55, 95%CI（-7.08，8.17），*P*=0.89，I^2=0%，T/C：51/45，极低质量证据]。

3 篇文献报道了不良反应，Meta 分析结果显示：雷公藤多苷片总不良反应发生率与环磷酰胺相当，16.84%（16/95） vs 20.0%（19/95），两组无统计学差异[RR=0.85，95%CI（0.46，1.55），*P*=0.59，I^2=0%，极低质量证据]。

5.6 慢性肾脏病患者，雷公藤多苷片联用环磷酰胺与单独使用环磷酰胺相比，哪个能使患者获益更多？

推荐意见：对于慢性肾脏病，不建议雷公藤多苷片与环磷酰胺联合使用，主要考虑联合用药虽然可降低 24 小时尿蛋白水平，但可能增加不良反应发生风险。（证据级别：极低；推荐强度：强反对）

使用条件：适用于以蛋白尿为主要表现的慢性肾脏病。

安全性：雷公藤多苷片联用环磷酰胺有增加不良反应发生风险的趋势，需要重点关注肝功能异常、胃肠道反应。

证据描述：

共纳入 3 篇文献，均为随机对照试验，研究对象均为肾病综合征，基础治疗均使用激素，环磷酰胺组的用药方法为常规推荐方法，疗程 8-12 个月。2 篇研究均报道了雷公藤多苷片联用环磷酰胺对 24 小时尿蛋白定量的影响。Meta 分析结果显示，联用组相较单用环磷酰胺组可进一步降低 24 小时尿蛋白定量［MD=−1.66，95%CI（−2.22，−1.10），*P*=0.05，I^2=74%，T/C=71/71，极低质量证据］。

3 篇文献均报道了不良反应，Meta 分析结果显示：联合用药总不良反应发生率升高，30.39%（31/101） vs 19.19%（19/99），两组无统计学差异[RR=1.5，95%CI（0.69，3.23），*P*=0.12，I^2=53%，极低质量证据]。亚组分析包括胃肠道反应[RR=1.11，95%CI（0.36，3.45），*P*=0.30，I^2=6%，极低质量证据]、肝功能异常[RR=2.11，95%CI（0.55，8.04），*P*=0.45，I^2=0%，极低质量证据]。

5.7 慢性肾脏病患者，单独使用雷公藤多苷片与钙调神经磷酸酶抑制剂（环孢素、他克莫司、西罗莫司）相比，哪个能使患者获益更多？

推荐意见：对于特发性膜性肾病，可选择使用雷公藤多苷片，降低 24 小时尿蛋白的程度与钙调神经磷酸酶抑制剂相当。（证据级别：低；推荐强度：条件性推荐）

使用条件：非继发性膜性肾病，且不伴有不适宜应用免疫抑制剂的其他疾病，如 HIV

感染、乙肝等。

安全性：与钙调神经磷酸酶抑制剂相比，雷公藤多苷片总不良反应发生率相对较低，尤其在空腹血糖异常和感染方面。

证据描述：

共纳入 5 篇文献，均为队列研究，研究对象均为特发性膜性肾病。报道 24 小时尿蛋白 3 篇、血肌酐 2 篇。Meta 分析结果显示：单用雷公藤多苷片与单用钙调神经磷酸酶抑制剂相比，降低 24 小时尿蛋白定量的程度无差异[MD=0.00，95%CI（-0.68，0.69），P=0.99，I^2=0%，T/C：83/92，低质量证据]。单用雷公藤多苷片与单用钙调神经磷酸酶抑制剂相比，降低血肌酐的程度无差异[MD=1.46，95%CI（-5.48，8.40），P=0.68，I^2=0%，T/C：60/62，低质量证据]。

共 4 篇文献报道不良反应，Meta 分析结果显示：雷公藤多苷片组不良反应发生率相对较低，31.8%（54/170） vs 47.5%（84/177），两组有统计学差异[RR=0.64，95%CI（0.49，0.84），P=0.001，I^2=0%，低质量证据]。亚组分析显示：雷公藤多苷片组的空腹血糖异常发生率较低，2.3%（1/43） vs 16.7%（8/48），二者有明显统计学差异[RR=0.18，95%CI（0.05，0.66），P=0.01，I^2=0%，低质量证据]。雷公藤多苷片组的感染发生率较低，23.6%（30/127） vs 43.4%（56/129），二者有明显统计学差异[RR=0.54，95%CI（0.38，0.77），P＜0.001，I^2=0%。低质量证据]

5.8 慢性肾脏病患者，雷公藤多苷片联用钙调神经磷酸酶抑制剂与单独使用钙调神经磷酸酶抑制剂相比，哪个能使患者获益更多？

推荐意见：可选择雷公藤多苷片联用钙调神经磷酸酶抑制剂治疗慢性肾脏病蛋白尿，其效果优于单用钙调神经磷酸酶抑制（证据级别：极低；推荐强度：条件性推荐）

使用条件：适用于单独使用钙调神经磷酸酶抑制剂 24 小时尿蛋白控制不佳者。

安全性：雷公藤多苷片联用钙调神经磷酸酶抑制剂，不增加总不良反应发生率。但需注意钙调神经磷酸酶抑制剂的剂量选择，需监测该类药物血药浓度。

证据描述：

共纳入文献 19 篇，其中随机对照试验 13 篇，队列研究 5 篇，病例对照研究 1 篇。结局指标方面，24 小时尿蛋白 12 篇，血肌酐 11 篇。Meta 分析结果显示：与单独使用钙调神经磷酸酶抑制剂相比，雷公藤多苷片联用钙调神经磷酸酶抑制剂可进一步降低 24 小时尿蛋白[MD=-0.86，95%CI（-0.92，-0.79），P＜0.01，I^2=83%，T/C：383/376，极低质量证据]。亚组分析显示，对于膜性肾病、肾病综合征、IgA 肾病、肾移植后蛋白尿等多种不同的慢性肾脏病类型，联合用药组降尿蛋白程度均优于钙调神经磷酸酶抑制剂单药治疗。血肌酐方面，与单独使用钙调神经磷酸酶抑制剂相比，联合用药可降低患者血肌酐[MD=-24.10，95%CI（-37.64，-10.55）， P＜0.01，I^2=97%，T/C：171/170，低证据质量）。

共 15 篇文献报道不良反应，Meta 分析结果显示：与单独使用钙调神经磷酸酶抑制剂相比，联合用药组不良反应发生率较低 13.8%（85/617） vs 35.0%（101/589），但无统计学差异[RR=0.81，95%CI（0.5，1.30），P＜0.01，I^2=67%，极低质量证据]。

5.9 对于肾病综合征蛋白尿患者，雷公藤多苷片单独使用或联用 ACEI/ARB/激素/免疫抑制剂与单独使用 ACEI/ARB/激素/免疫抑制剂相比，哪个能使患者受益更多？

推荐意见：对于肾病综合征患者，在纠正低蛋白血症的前提下，可选择雷公藤多苷片与 ACEI/ARB/激素/免疫抑制剂（环磷酰胺除外）联用，降尿蛋白的效果优于单用 ACEI/ARB/激素/免疫抑制剂（证据级别：极低；推荐强度：强推荐）

使用条件：适用于激素抵抗或者难治性肾病综合征。

安全性：与单独使用 ACEI/ARB/激素/免疫抑制剂相比，联合用药不增加总不良反应发生率。

证据描述：

共纳入文献 23 篇，均为随机对照试验，报道 24 小时尿蛋白 22 篇、血肌酐 16 篇、尿素氮 11 篇。Meta 分析结果显示：雷公藤多苷片联合用药组，能进一步降低 24 小时尿蛋白定量，二者差异有统计学意义[MD=-0.81，95%CI（-0.97，-0.66），P＜0.001，I^2=89%，T/C：1006/1034，极低质量证据]。雷公藤多苷片联合用药组，能进一步降低血肌酐，二者差异有统计学意义[MD=-8.79，95%CI（-11.41，-6.17），P＜0.001，I^2=71%，T/C：790/776，极低质量证据]。雷公藤多苷片联合用药组，能进一步降低尿素氮[MD=-0.57，95%CI（-0.86，-0.27），P＜0.001，I^2=86%，T/C：535/520，极低质量证据]。与对照组相比，联合用药组可升高血浆白蛋白水平[MD=4.24，95%CI（2.63，5.84），P＜0.001，I^2=95%，极低质量证据]。联合用药组可进一步降低疾病复发率[OR=0.16，95%CI（0.05，0.5），P=0.001，I^2=0%，极低质量证据]。

13 篇文献报道了不良反应，联合用药不良反应发生率相对较低，16.06%（75/467） vs 28.48%（127/446），两组具有统计学差异[OR=0.47，95%CI（0.34，0.65），P＜0.001，I^2=7%，低质量证据]，雷公藤多苷片联合用药组消化道不良反应较低 7.81%（31/397） vs 14.18%（55/388）。

5.10 慢性肾脏病患者在使用雷公藤多苷片出现轻度肝功能异常（ALT 或 AST＜3 倍正常值上限），立即停用雷公藤多苷片与继续使用雷公藤多苷片联合保肝药相比，哪个获益更多？

推荐意见：对于慢性肾脏病患者，在使用雷公藤多苷片时出现转氨酶升高（ALT 或 AST＜3 倍正常值上限），可联合保肝药，若监测转氨酶无明显下降，则停用雷公藤多苷片。（专家共识；推荐强度：条件性推荐）

使用条件：适用于基础肝功能正常的患者。

安全性：雷公藤多苷片有潜在肝损伤风险，用药期间需要加强肝功能监测。

证据描述：

目前未见有关慢性肾脏病患者在使用雷公藤多苷片出现轻度肝功能异常（ALT 或 AST＜3 倍正常值上限），停用雷公藤多苷片与继续使用雷公藤多苷片联合保肝药相比的临床研究，因此只能进行描述性的统计。已有的 64 个关于雷公藤多苷片的 RCT 研究中，有 2482 人使

用了雷公藤多苷片，其中 165 例出现了肝功能异常，大多为轻度。其中有 136 例采用了继续使用雷公藤多苷片，同时联合保肝药，占 82.42%；有 14 例在使用保肝药的同时采用减量处理，还有 8 例停用了雷公藤多苷片，另外的 7 例未表明具体的处理措施。从中可见，使用雷公藤多苷片后出现肝酶升高，大多采用继续治疗并联用保肝药，而且不影响最后治疗效果。针对此问题，本项目组设计了 1 轮专家问卷，调查临床专家在使用雷公藤多苷片出现轻度肝功能异常（ALT 或 AST＜3 倍正常值上限）时的处理方法。问卷共发放共识组 15 位临床专家，7 名专家（46.67%）考虑减量或其他治疗处理，6 名专家（40%）选择立即停用雷公藤多苷片，2 名（13.33%）专家建议雷公藤多苷片减量。

5.11 慢性肾脏病长期服用雷公藤多苷片的育龄期女性患者，停药 3 个月与停药 6 个月相比，患者备孕条件哪个更好？

推荐意见：对于长期服用雷公藤多苷片的慢性肾脏病女性育龄期患者，如有生育需求，建议停药 6 个月以上再备孕。（专家共识；推荐强度：条件性推荐）

使用条件：对于育龄期女性，在服用雷公藤多苷片之前，应充分告知该药物的生殖毒性，取得患者知情同意后方可使用。

安全性：雷公藤多苷片可引起月经紊乱、闭经、性欲减退，甚至不孕。

证据描述：

雷公藤多苷片常见女性生殖系统不良反应，对于育龄期女性，停药多长时间可备孕/怀孕，目前尚无相应的文献报道。本项目组设计了一轮专家问卷，调查临床专家在对育龄期女性使用雷公藤多苷片时，停药多长时间可怀孕。问卷共发放共识组专家 15 名，排除 3 名无此方面用药经验的专家，有效问卷 12 份，10 名（83.33%）专家建议＞6 个月，1 名（8.33%）专家建议＞3 个月，1 名（8.33%）专家建议在女性激素正常后可备孕。

5.12 慢性肾脏病长期服用雷公藤多苷片的育龄期男性患者，停药 3 个月与停药 6 个月相比，患者备孕条件哪个更好？

推荐意见：对于长期服用雷公藤多苷片的慢性肾脏病男性育龄期患者，如有生育需求，建议停药 6 个月以上再备孕。（专家共识；推荐强度：条件性推荐）

使用条件：对于育龄期男性，在服用雷公藤多苷片之前，应充分告知该药物的生殖毒性，取得患者知情同意后方可使用。

安全性：雷公藤多苷片可引起精子活力下降、数量减少、形态变化、睾丸萎缩、性欲减退、生育能力下降或不育。

证据描述：

雷公藤多苷片常见男性生殖系统不良反应，对于育龄期男性，停药多长时间可备孕，目前尚无相应的文献报道。本项目组设计了一轮专家问卷，调查临床专家在对育龄期男性使用雷公藤多苷片时，停药多长时间可怀孕。问卷共发放共识组专家 15 名，排除 3 名无此方面用药经验的专家，有效问卷 12 份，8 名（66.67%）专家建议＞6 个月，2 名（16.67%）专家建议＞3 个月，2 名（16.67%）专家建议在精液常规正常后可备孕。

5.13 雷公藤多苷片是由肝脏代谢的药物，对肝药酶有抑制作用，当与其它经肝药酶代谢的

药物联用时，如利福平、酮康唑等，有可能对雷公藤多苷片治疗慢性肾脏病的疗效和安全性产生什么样的影响？

推荐意见：雷公藤多苷片与其他经 CYP3A4 代谢的药物同时使用时，可能会产生药物相互作用，需加强临床疗效和不良反应监测。（专家共识；推荐强度：强推荐）

使用条件：雷公藤多苷片主要经由细胞色素 P450 酶系中的 CYP3A4 代谢。从药理学角度，强 CYP3A4 抑制剂会升高雷公藤多苷片血药浓度，可能引发毒性；强 CYP3A4 诱导剂会降低雷公藤多苷片疗效。

安全性：目前尚无雷公藤与其他经 CYP3A4 代谢药物同时使用的安全性评价文献报道。

证据描述：体外实验表明雷公藤多苷对 CYP3A4、CYP2C9、CYP2C19 均有调控作用，可不同程度地抑制相应酶活性，其中对 CYP3A4 的抑制与浓度相关。雷公藤多苷片对 CYP3A4 的强抑制作用，不仅与雷公藤的肝毒性有关，也在雷公藤与其他药物合用时带来了药物－药物相互作用的风险。

附录 A

（资料性）

利益冲突情况

本文件制定过程中“无利益冲突”，所有参与本文件制定的成员均和药品生产企业没有任何经济利益往来。

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Foreword

Please note that some content in this document may involve patents. The publishing body assumes no responsibility for identifying patents.

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Introduction

The rising prevalence of chronic kidney disease (CKD) represents a significant global public health challenge.Since Prof. Li Leishi et al. first pioneered the use of Tripterygium extracts to treat glomerulonephritis in 1981, Tripterygium Wilfordii Polyglycosides Tablets (TWPs) have been widely used for treating various CKD, including chronic glomerulonephritis, IgA nephropathy, lupus nephritis, Henoch–Schönlein purpura nephritis, diabetic kidney disease, and others. TWPs exert their therapeutic effects in CKD through multiple mechanisms. Primarily, they alleviate local renal inflammation by suppressing signaling pathways such as nuclear factor kappa-B (NF-κB), thereby reducing the expression of inflammatory factors including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) . Furthermore, they modulate the T-lymphocyte subset ratio and B-cell function, inhibiting the deposition of immune complexes. Additionally, these tablets upregulate the expression of key podocyte proteins such as Nephrin and Podocin, which helps stabilize the cytoskeleton. These combined actions contribute to reducing proteinuria and delaying the progression of glomerulosclerosis. Compared with other immunosuppressants, TWPs are relatively inexpensive, imposing a smaller economic burden on patients. TWPs have been included in the 2018 National Essential Drug List and the 2020 Class A National Medical Insurance Drug List, and they are incorporated in several Chinese CKD-related guidelines. In practice, the clinical use of TWPs in nephrology has, to some extent, exceeded the indications specified in the package insert, supported by a large amount of clinical research. In the treatment of CKD proteinuria, TWPs are often combined with Angiotensin-Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs), glucocorticoids, calcineurin inhibitors, and other drugs. However, systematic research on the benefits and risks of combining TWPs with these agents is lacking. Moreover, TWPs have toxicities affecting liver, kidney, blood, and reproductive systems: In the kidney, they trigger apoptosis of renal tubular epithelial cells and interstitial inflammation, leading to acute kidney injury. In the liver, oxidative stress damages hepatocytes, resulting in drug-induced hepatitis. Within the hematopoietic system, TWPs suppress bone marrow function, which can cause leukopenia or thrombocytopenia . For the reproductive system, they interfere with sex hormone synthesis and the maturation of germ cells, leading to amenorrhea in females and reduced sperm motility in males. Notably, the renal damage induced by TWPs is often reversible, contrasting with the chronic fibrosis typically associated with aristolochic acid, yet close monitoring remains essential. Inappropriate use of TWPs can increase the risk of adverse reactions, especially in special populations such as those with liver dysfunction or reproductive-age patients with fertility needs. Therefore, questions about how to rationally apply TWPs in CKD treatment and how its efficacy and adverse risk compare to other drugs are urgent clinical issues.

This document is grounded in clinical practice and evidence-based research on the safe use of TWPs in CKD. Following the principle of "evidence first, consensus as auxiliary, experience as reference," it is based on the best existing evidence and broad consensus to form recommendations for TWPs in CKD. This ensures that the guidelines are scientific, practical, and clinically operable, guiding Traditional Chinese Medicine (TCM) and Western clinicians in the standardized use of TWPs to treat CKD. The goals are to improve clinical efficacy, reduce adverse events, guide pharmacists in their practice to achieve optimal patient education, enhance patient quality of life, and save medical resources.

Guidelines for Rational Use of Tripterygium Wilfordii Polyglycosides Tablet in the Treatment of Chronic Kidney Disease

1 Scope

This document specifies the pre-use evaluation, indications, dose selection, efficacy evaluation, contraindications, drug interactions, usage precautions, and adverse reactions for the clinical use of TWPs in CKD treatment.

It applies to guiding clinicians and pharmacists in the safe use of TWPs for CKD.

2 Normative References

The content of the documents listed below, through normative references in this text, constitutes essential provisions of this document. For dated references, only the edition corresponding to the date is applicable; for undated references, the latest edition (including amendments) applies.

International Classification of Diseases for Mortality and Morbidity Statistics (Eleventh Revision) (ICD-11)

3 Terms and Definitions

The following terms and definitions apply to this document.

3.1 Tripterygium Wilfordii Polyglycosides

A highly polar, lipid-soluble mixture extracted and purified from the dried roots and rhizomes of *Tripterygium wilfordii* Hook. f. (Celastraceae family).

Note: Major active components include diterpenes, triterpenes, alkaloids, etc.

3.2 Tripterygium Wilfordii Polyglycosides Tablets (TWPs)

Light yellow to brownish-yellow tablets made from Tripterygium Wilfordii polyglycosides.

Note 1: Slightly bitter and astringent. They function to dispel wind and detoxification, eliminate dampness and reduce swelling, relax tendons and activate collaterals. They exert anti-inflammatory and immunosuppressive actions (suppressing both cellular and humoral immunity). They are used for rheumatoid arthritis of wind-heat stagnation and blood stasis type, nephrotic syndrome, Behçet's disease, lepra reaction, autoimmune hepatitis, and similar conditions.

3.3 Chronic Kidney Disease (CKD)

Structural and/or functional abnormalities of the kidneys persisting for over 3 months, due to various causes.

3.4 Nephrotic Syndrome

A clinical syndrome caused by various etiologies, characterized by heavy proteinuria (≥3.5 g/24h), hypoalbuminemia (<30 g/L), edema, and/or hyperlipidemia.

4 Overview

The "Clinical Management Guidelines for Delaying the Progression of CKD (2025 edition)" recommend minimizing and reducing proteinuria as far as patients can tolerate, ideally until urine tests become negative. TCM plays an important role in CKD treatment, among which TWPs are recognized as a single herbal extract with a clear effect on reducing proteinuria and are widely used clinically.

Pharmacological studies indicate that TWPs have immunosuppressive-like effects. Basic research has gradually elucidated mechanisms such as inhibition of glomerular mesangial cell and matrix proliferation, improvement of glomerular filtration membrane permeability, and reduction of podocyte injury.

5 Recommendations and Evidence

5.1 For patients with CKD, would combination therapy with TWPs and ACEI/ARBs provide greater benefit compared with ACEI/ARBs alone?

Recommendation: We recommend TWPs combined with ACEI/ARBs to reduce proteinuria in CKD patients; this combination is superior to ACEI/ARBs alone (evidence level: very low; recommendation strength: strong).

TWPs combined with ACEI/ARBs also further reduce serum creatinine and blood urea nitrogen (BUN), likely related to improved proteinuria (evidence level: very low; recommendation strength: conditional).

Applicable Conditions: Applicable to diabetic nephropathy, chronic glomerulonephritis, and IgA nephropathy.

Safety: Compared with ACEI/ARBs alone, combining TWPs increases the overall incidence of adverse reactions. The main side effects are menstrual disorders and amenorrhea in women, impotence in men, elevated alanine aminotransferase (ALT) / aspartate aminotransferase (AST), and decreases in white blood cells and platelets.

Evidence:

A total of 96 studies were included (88 studies reported 24h urinary protein, 79 studies reported serum creatinine, 36 studies reported BUN). Meta-analysis showed that TWPs+ACEI/ARBs compared with ACEI/ARBs alone further

reduced 24h urinary protein excretion [MD=-0.55, 95% CI (-0.58, -0.52), *P*<0.001, I^2=99%，T/C：4725/4641， (very low-quality evidence)]. Subgroup analysis by CKD type indicated that for diabetic nephropathy, chronic glomerulonephritis, and IgA nephropathy, the combined therapy group had superior protein reduction. The combination group further reduced serum creatinine level compared with control group[MD=-15.55, 95% CI (-20.09, -11.01), P<0.001, I^2=99.8%，T/C：4915/5086， (very low-quality evidence)]. The combination group further reduced BUN level [MD=-1.04, 95% CI (-1.89, -0.19), P=0.008, I^2=99.5%，T/C:1853/1802， (very low-quality evidence)].

Eighty-five studies reported adverse events (76 RCTs, 9 cohort studies). Meta-analysis showed higher adverse event rate in the combined group (10.7% (368/3441）vs 6.3%(202/3208））; [RR=1.39, 95% CI（1.14，1.71）, *P*<0.001, I^2=15.3%， (low-quality evidence)];. Subgroup analysis revealed significantly higher reproductive system adverse events in the combined group (8.89%（56/630）vs 0.35%（2/579）; [RR=5.52，95%CI(2.03，15.04）, *P*<0.01,I^2=0%; (very low-quality evidence)]. The combined group also had a slightly higher incidence of liver function abnormalities (5.73%（134/2338）vs 1.10%（25/2273）; [RR=1.52，95%CI(1.07，3.57）, *P*<0.001，I^2=0%， (low-quality evidence)]; and higher hematological adverse reactions (leukopenia, thrombocytopenia, eosinophilia): 4.17%（82/1966）vs 1.44%（28/1937）; [RR=3.57，95%CI(2.39，5.33）, *P*<0.001，I^2=21.8%，(low-quality evidence)]; .

5.2 For patients with CKD, would using TWPs alone provide greater benefit compared with ACEI/ARBs alone?

Recommendation: TWPs alone can be used to treat CKD proteinuria, and its effect is comparable to that of ACEI/ARBs (evidence level: very low; recommendation strength: conditional).

Both TWPs and ACEI/ARBs can slightly reduce serum creatinine and BUN, possibly due to improved proteinuria (evidence level: very low; recommendation strength: conditional).

Applicable Conditions: Consider TWPs especially if ACEI/ARBs are contraindicated (e.g., hyperkalemia, bilateral renal artery stenosis) or if the patient has experienced serious ACEI/ARBs adverse effects (e.g., hypotension, dry cough).

Safety: Compared with ACEI/ARBs, TWPs do not increase the overall incidence of adverse reactions. The primary side effects include menstrual disorders and amenorrhea in women, impotence in men, elevated ALT/AST, and decreases in white blood cell or platelet counts.

Evidence:

A total of 16 studies were included (15 randomized controlled trials, 1 prospective cohort, 1 Meta-analysis). Outcomes reported included 24h urinary protein (13 studies), serum creatinine (12 studies), and BUN (11 studies).

Meta-analysis: TWPs alone compared with ACEI/ARBs alone, further reduced 24h urinary protein excretion [MD=-0.40, 95% CI (-0.58, -0.21), P<0.001, I^2=96%, T/C： 508/492, (very low-quality evidence)]. Both treatments showed a trend toward slight reduction in serum creatinine [MD=-3.38, 95% CI (-8.75, 3.96), P=0.46, I^2=94% ， T/C ： 468/460, (very low-quality evidence)] and BUN [MD=-2.29,95%CI(-3.74,-0.84),P<0.01,I^2=97%, T/C:222/218, (very low-quality evidence)].

There are 8 studies reported adverse events. Meta-analysis showed a slightly higher adverse rate in the TWPs group (12.1%(33/273) vs 11.0%(29/263)), but this difference was not statistically significant [OR=1.09, 95% CI (0.43, 2.73), *P*=0.86, I^2=39%; (very low-quality evidence)]. Subgroup analysis found a higher incidence of gastrointestinal adverse events in the TWPs group (6.7% vs 0.0%）; [RR=4.60，95%CI（1.33，15.87），Z=2.42，*P*=0.02，I^2=0%，T/C：195/183，（evidence very low)].

5.3 For patients with CKD, would using TWPs alone provide greater benefit compared with glucocorticoids alone?

Recommendation: In certain cases, TWPs alone may be used to treat CKD proteinuria, and its effect can be superior to glucocorticoids (evidence level: very low; recommendation strength: strong).

Applicable Conditions: For CKD patients with diabetic nephropathy, glucocorticoids-induced diabetes, or other contraindications to glucocorticoids, or for those concerned about glucocorticoids adverse effects (such as obesity, cataracts, avascular necrosis of the femoral head), or glucocorticoids-resistant cases, TWPs may be considered before glucocorticoids.

Safety: Compared to glucocorticoids, TWPs alone have a lower overall adverse reaction rate. In particular, infection rates were lower in the TWPs group, while rates of gastrointestinal, hematological, reproductive, endocrine, and skin adverse reactions were similar between TWPs and glucocorticoids.

Evidence:

Seven randomized controlled trials (RCTs) were included (24h urinary protein: 2 studies; serum creatinine: 3 studies; BUN: 3 studies). Meta-analysis: TWPs compared with glucocorticoids showed a trend toward further reduction in 24h urinary protein [MD=-0.95,95%CI(-1.88, -0.02),*P*=0.05,I^2=90%，T/C：291/270，(very low-quality evidence)]. Both treatments tended to slightly reduce serum creatinine [MD=-12.99, 95% CI (-31.94, 5.96), P=0.18, I^2=37%，T/C：126/107，(evidence low)] and BUN [MD=-1.11, 95% CI (-2.65, 0.43), P=0.16, I^2=92%,T/C:126/107,(low-quality evidence)].

Six studies reported adverse events: TWPs group had a 40.2%(117/291) adverse rate vs 84.1%(227/270) for glucocorticoids (significantly lower) [RR=0.48, 95% CI (0.38, 0.61), P<0.001, I^2=2%， （evidence low）]. Subgroup analysis: infection incidence was lower in the TWPs group (3.9% vs 9.7%) [RR=0.37, 95% CI (0.14, 0.97), P=0.04， I^2=0%， T/C： 6/13， (low-quality

evidence)].

5.4 For patients with CKD, would combination therapy with TWPs and glucocorticoids provide greater benefit compared with glucocorticoids alone?

Recommendation: TWPs combined with glucocorticoids may be chosen to treat CKD proteinuria, and this combination is superior to glucocorticoids alone (evidence level: very low; recommendation strength: strong).

Applicable Conditions: Suitable for patients whose proteinuria is not adequately controlled by glucocorticoids alone.

Safety: No increase in adverse reactions was observed with the combined therapy compared to glucocorticoids alone.

Evidence:

A total of 62 RCTs were included (24h urinary protein: 48 studies; serum creatinine: 30 studies; BUN: 18 studies). Meta-analysis: TWPs + glucocorticoids compared with glucocorticoids alone further reduced 24h urinary protein [MD=-0.62, 95% CI (-0.70, -0.55), P<0.001, I^2=92%， T/C： 1851/1846， (low-quality evidence)]. Combined therapy further reduced protein at all levels. It also showed a slight further decrease in serum creatinine [MD=-9.92, 95% CI (-13.27, -6.56), P<0.001, I^2=91%，T/C：1051/1047， (low-quality evidence)] and BUN [MD=-0.79, 95% CI (-1.03, -0.55), P<0.001, I^2=71%,T/C： 701/700， (low-quality evidence)].

A total of 30 RCTs reported adverse events: combined group 13.4%(155/1158) vs glucocorticoids alone 17.9%(203/1137), [RR=0.70, 95% CI (0.43, 1.14), *P*<0.001, I^2=86%].

5.5 For patients with CKD, would using TWPs alone provide greater benefit compared with cyclophosphamide alone?

Recommendation: On the basis of glucocorticoid use, TWPs are recommended for CKD treatment, owing to a similar reduction in proteinuria levels compared with cyclophosphamide (evidence level: very low; recommendation strength: conditional).

Applicable Conditions: Suitable for patients whose proteinuria is not adequately reduced by glucocorticoids alone.

Safety: Compared with cyclophosphamide, TWPs do not increase the overall adverse reaction rate. The main adverse reactions of TWPs include liver function abnormalities, leukopenia, and gastrointestinal reactions.

Evidence:

Eight studies were included (6 RCTs, 2 cohort studies), all in nephrotic syndrome patients, with glucocorticoids as a basic treatment. The TWPs dose did not exceed the label recommendation; cyclophosphamide was dosed

conventionally. Treatment duration ranged from 1 to 18 months. Outcomes reported included 24h urinary protein (6 studies) and serum creatinine (2 studies). Meta-analysis: TWPs group showed a non-significant trend toward further reduction in 24h urinary protein [MD=-0.09，95%CI(-0.54,0.36),*P*=0.71，I^2=96%，T/C：207/199， (very low-quality evidence)] and a similar trend in serum creatinine [MD=0.55, 95% CI (-7.08, 8.17), P=0.89, I^2=0%, T/C：51/45，,(very low-quality evidence)].

Three studies reported adverse events: total adverse rates were similar (16.84%（16/95） for TWPs vs 20.00% （19/95）for cyclophosphamide, [RR=0.85，95%CI=0.46，1.55，*P*=0.59，I^2=0%，(evidence very low)].

5.6 For patients with CKD, would combination therapy with TWPs and cyclophosphamide provide greater benefit compared with cyclophosphamide alone?

Recommendation: For CKD, we strongly recommend against combining TWPs with cyclophosphamide. Although the combination can reduce 24h urinary protein, it may increase the risk of adverse reactions (evidence level: very low; Recommendation strength: strong against).

Applicable Conditions: This recommendation applies to CKD patients with proteinuria as a primary concern.

Safety: Combination therapy with TWPs and cyclophosphamide tends to increase the risk of adverse reactions, and particular attention should be paid to abnormal liver function and gastrointestinal reactions.

Evidence:

Three RCTs were included, all in nephrotic syndrome patients on glucocorticoid background, with cyclophosphamide dosed conventionally for 8–12 months. Two studies reported the effect on 24h urinary protein: the TWPs+CTX group further reduced 24h urinary protein [MD=-1.66, 95% CI (-2.22, -1.10), P=0.05, I^2=74%,T/C=71/71，(very low-quality evidence)] .

Three studies reported adverse events: Meta-analysis showed higher total adverse in the combination group (30.39% （31/101） vs 19.19%（19/99）,[RR=1.5，95%CI(0.69，3.23)，*P*=0.12，I^2=53%,(very low-quality evidence)]. Subgroup: gastrointestinal [RR=1.11，95%CI(0.36,3.45)，*P*=0.30，I^2=6%,(very low-quality evidence)]] and liver [RR=2.11，95%CI(0.55,8.04)，*P*=0.45，I^2=0%，(very low-quality evidence)].

5.7 For patients with CKD, would using TWPs alone provide greater benefit compared with calcineurin inhibitors (cyclosporine, tacrolimus, sirolimus) alone?

Recommendation: For idiopathic membranous nephropathy, TWPs can be chosen; the reduction in 24h urinary protein is comparable to that achieved by calcineurin inhibitors (evidence level: low; recommendation strength: conditional).

Applicable Conditions: Applicable to idiopathic (non-secondary) membranous nephropathy patients who do not have other contraindications to immunosuppressants (e.g., HIV infection, hepatitis B, etc.).

Safety: Compared with calcineurin inhibitors, TWPs had a relatively lower overall adverse event rate, mainly manifesting as impaired fasting glucose and infection.

Evidence:

Five cohort studies were included, all in idiopathic membranous nephropathy. Outcomes: 24h urinary protein (3 studies), serum creatinine (2 studies). Meta-analysis: TWPs alone compared with calcineurin inhibitor showed no difference in 24h urinary protein reduction [MD=0.00, 95% CI (-0.68, 0.69), P=0.99, I^2=0%,T/C： 83/92,(low-quality evidence)] and no difference in serum creatinine [MD=1.46, 95% CI (-5.48, 8.40), P=0.68, I^2=0%, T/C： 60/62， (low-quality evidence)].

Four studies reported adverse events: the TWPs group had a lower adverse rate 31.8% (54/170) vs 47.5%(84/177); [RR=0.64, 95% CI 0.49–0.84, P=0.001, I^2=0%,T/C： 60/62， (low-quality evidence)]. Subgroup: TWPs group had a significantly lower rate of impaired fasting glucose (2.3%（1/43） vs 16.7%（8/48）;[RR=0.18，95%CI（0.05，0.66），Z=2.58，P=0.01，I^2=0%，(low-quality evidence)]and lower infection rate 23.6%（30/127） vs 43.4%（56/129）; [RR=0.54，95%CI（0.38，0.77），Z=3.41，P＜0.001，I^2=0%,(low-quality evidence)].

5.8 For patients with CKD, would combination therapy with TWPs and calcineurin inhibitors provide greater benefit compared with calcineurin inhibitors alone?

Recommendation: TWPs combined with calcineurin inhibitors can be chosen to treat CKD proteinuria, and this combination is superior to calcineurin inhibitors alone (evidence level: very low; recommendation strength: conditional).

Applicable Conditions: Applicable to patients on calcineurin inhibitors whose 24h urinary proteinuria remains inadequately controlled.

Safety: Combining TWPs with calcineurin inhibitors did not increase the total incidence of adverse reactions. However, attention must be paid to calcineurin inhibitor dosing; blood drug concentration should be monitored.

Evidence:

A total of 19 studies were included (13 RCTs, 5 cohort, 1 case-control). Outcomes: 24h urinary protein (12 studies), serum creatinine (11studies). Meta-analysis: TWPs+calcineurin vs calcineurin alone further reduced 24h urinary protein [MD=-0.86, 95% CI (-0.92, -0.79), P<0.01, I^2=83%,T/C：383/376，(very low-quality evidence)] . Subgroup analysis showed that for membranous nephropathy, nephrotic syndrome, IgA nephropathy, post-transplant proteinuria, and other CKD types, the combined group consistently had greater protein

reduction. For serum creatinine, the combination significantly reduced creatinine in nephrotic syndrome patients [MD=-24.10, 95% CI (-37.64, -10.55), P<0.01, I^2=97%,T/C：171/170,(low-quality evidence)].

A total of 15 studies reported adverse events: combined therapy had a lower adverse rate 13.8%(85/617) vs 35.0%(101/589); [RR=0.81，95%CI（0.5，1.30），*P*<0.01，I^2=67%,（evidence very low)].

5.9 For patients with nephrotic syndrome, would using TWPs (alone or with ACEI/ARBs/glucocorticoids/immunosuppressant) provide greater benefit compared with ACEI/ARBs/glucocorticoids/immunosuppressant alone?

Recommendation: For nephrotic syndrome patients, after amelioration of hypoproteinemia, TWPs combined with ACEI/ARBs/glucocorticoids/immunosuppressant (cyclophosphamide excluded) may be chosen; the proteinuria reduction effect is superior to ACEI/ARBs/glucocorticoids/immunosuppressant alone (evidence level: very low; recommendation strength: strong).

Applicable Conditions: Applicable to glucocorticoids-resistant or refractory nephrotic syndrome.

Safety: Compared with ACEI/ARBs/glucocorticoids/immunosuppressant alone, combined therapy did not increase the total incidence of adverse reactions.

Evidence:

A total of 23 RCTs were included, reporting 24h urinary protein (22 studies), serum creatinine (16 studies), and BUN (11 studies). Meta-analysis: TWPs combination compared with control treatments further reduced 24h urinary protein [MD=-0.81, 95% CI (-0.97, -0.66), *P*<0.001, I^2=89%,T/C： 1006/1034, (very low-quality evidence)]. Combined therapy further reduced creatinine [MD=-8.79, 95% CI (-11.41, -6.17), *P*<0.001, I^2=71%,T/C： 790/776,(very low-quality evidence)] and BUN [MD=-0.57, 95% CI (-0.86, -0.27), *P*<0.001, I^2=86%,T/C： 535/520,(very low-quality evidence)]. Plasma albumin was increased in the combined group [MD=4.24, 95% CI (2.63, 5.84), *P*<0.001, I^2=95%, (very low-quality evidence)]. The recurrence rate was significantly lower in the combined group [OR=0.16, 95% CI (0.05, 0.50), *P*=0.001, I^2=0%, (very low-quality evidence)].

A total of 13 studies reported adverse events: the combined group had a lower adverse rate 16.06%(75/467) vs 28.48%(127/446); [OR=0.47，95%CI（0.34，0.65），Z=4.6，*P*<0.001，I^2=7%，(low-quality evidence)], mainly gastrointestinal reactions 7.81%（31/397） vs 14.18%（55/388）.

5.10 If a CKD patient using TWPs develops mild liver function abnormality (ALT or AST less than 3 times high than the upper limit of normal value (ULN)), is it more beneficial to stop TWPs immediately or continue TWPs with hepatoprotective agents?

Recommendation: For CKD patients who develop elevated transaminases (ALT or AST <3× ULN) while on TWPs, one may continue TWPs with hepatoprotective agents; if monitored transaminases do not significantly decrease, then discontinue TWPs (expert consensus; recommendation strength: conditional).

Applicable Conditions: Applicable to patients with normal baseline liver function.

Safety: TWPs have potential hepatotoxicity risk; liver function should be closely monitored during treatment.

Evidence:

There are no clinical studies comparing the outcomes between discontinuing TWPs and continuing TWPs combined with hepatoprotective agents in CKD patients who developed mild liver function abnormalities (ALT or AST <3× ULN) during TWPs treatment. Only descriptive statistics can be conducted: Descriptive data from 64 RCTs (2482 patients on TWPs) found 165 cases of liver injury, mostly mild. Among these, 136 patients (82.4%) continued TWPs with hepatoprotective agents, 14 patients (8.5%) reduced the TWPs dose and used hepatoprotectants, 8 patients (4.8%) discontinued TWPs, and 7 cases had unspecified management. This suggests that when liver enzyme rises, the majority of cases adopt continued treatment combined with hepatoprotective agents, and this approach does not affect the final treatment outcome.. To address this issue, we designed an expert questionnaires (including 15 nephrology experts) to investigate the management approaches adopted by clinical experts when mild liver function abnormalities (ALT or AST <3× ULN) occur during the administration of TWPs. Among them, 7 experts (46.67%) considered dose reduction or other interventions, 6 experts (40%) suggested discontinue TWPs immediately, and 2 experts (13.33%) recommended dose reduction.

5.11 For female CKD patients of childbearing age who have used TWPs long-term, which is better for pregnancy preparation: stopping medication for 3 months or 6 months?

Recommendation: For female CKD patients of childbearing age who have used TWPs long-term and wish to conceive, it is recommended to stop TWPs for more than 6 months before attempting pregnancy (expert consensus; recommendation strength: conditional).

Applicable Conditions: For women of reproductive age, the reproductive toxicity of TWPs should be fully explained, and informed consent obtained before use.

Safety: TWPs can cause menstrual disorders, amenorrhea, decreased libido, and even infertility.

Evidence:

There are no studies directly on how long female TWPs users should stop the drug before pregnancy. The project team designed a round of expert questionnaires to investigate how long clinical experts recommend discontinuing TWPs before pregnancy when the medication is administered to women of childbearing age. A total of 15 experts were distributed the questionnaire; 3 experts without medication experience in this aspect were excluded, resulting in 12 valid questionnaires. Among the valid responses, 10 experts (83.33%) recommended a discontinuation period of > 6 months, 1 expert (8.33%) suggested > 3 months, and 1 expert (8.33%) advised that pregnancy preparation could start after the woman's sex hormones return to normal..

5.12 For male CKD patients of childbearing age who have used TWPs long-term, which is better for pregnancy preparation: stopping medication for 3 months or 6 months?

Recommendation: For male CKD patients of childbearing age who have used TWPs long-term and wish to conceive, it is recommended to stop TWPs for more than 6 months before attempting pregnancy (expert consensus; recommendation strength: conditional).

Applicable Conditions: For men of reproductive age, the reproductive toxicity of TWPs should be fully explained, and informed consent obtained before use.

Safety: TWPs can cause decreased sperm motility, reduced sperm count, abnormal sperm morphology, testicular atrophy, decreased libido, and reduced fertility or infertility.

Evidence:

There are no studies on how long male TWPs users should stop the drug before conceiving. The project team designed a round of expert questionnaires to investigate how long clinical experts recommend discontinuing TWPs before pregnancy when the medication is administered to men of childbearing age. A total of 15 experts were distributed the questionnaire; 3 experts without medication experience in this aspect were excluded, resulting in 12 valid questionnaires. Among the valid responses, 8 experts (66.67%) recommended a discontinuation period of > 6 months, 2 experts (16.67%) suggested > 3 months, and 2 experts (16.67%) advised that pregnancy preparation could start after the outine semen analysis returns to normal.

5.13 What is the impact on TWPs efficacy and safety when TWPs (metabolized by the liver) are co-administered with other CYP3A4-metabolized drugs (e.g., rifampin, ketoconazole)?

Recommendation: Concurrent use of TWPs with other CYP3A4-metabolized

drugs may result in drug–drug interactions; clinical efficacy and adverse reactions should be closely monitored (expert consensus; recommendation strength: strong).

Applicable Conditions: TWPs are mainly metabolized by cytochrome P450 enzyme CYP3A4. Pharmacologically, strong CYP3A4 inhibitors will increase TWPs blood concentration (risking toxicity), and strong CYP3A4 inducers will decrease TWPs efficacy.

Safety: No safety evaluation literature on co-administration of TWPs with other CYP3A4-metabolized drugs is currently available.

Evidence:

In vitro studies show that TWPs modulate CYP3A4, CYP2C9, and CYP2C19 activities to varying degrees. TWPs can inhibit these enzymes, particularly a concentration-dependent inhibition of CYP3A4. The strong inhibition of CYP3A4 by TWPs is associated with its hepatotoxicity and poses a risk of drug–drug interactions when TWPs are used with other drugs.

ANNEX A
(Informative)
Conflict of Interest

No conflicts of interest were reported in the development of this document; all members involved in its drafting have no financial interests with pharmaceutical manufacturers.

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