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METHOTREXATE-FOLATE INTERPLAY: FROM PHARMACOLOGICAL MECHANISMS TO CLINICAL TOXICITY MANAGEMENT

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ABSTRACT

Methotrexate (MTX) is an established therapeutic agent used extensively in oncology and the management of chronic inflammatory and autoimmune disorders. Despite its clinical effectiveness, MTX may produce adverse effects involving the gastrointestinal tract, liver, bone marrow, and other rapidly dividing tissues. Many of these toxicities are associated with interference with folate-dependent metabolic pathways. Folate supplementation has therefore become an important strategy for improving the safety and tolerability of MTX therapy. This review examines the pharmacological basis of the interaction between MTX and folate, the clinical benefits of folic acid supplementation, and the role of folinic acid in the management of MTX toxicity. MTX inhibits dihydrofolate reductase and, following intracellular polyglutamation, affects several folate-dependent pathways involved in nucleotide synthesis and cellular metabolism. In low-dose MTX therapy, additional mechanisms, including altered purine metabolism and adenosine signalling, contribute to its anti-inflammatory effects. Evidence from clinical studies and systematic reviews indicates that folic acid supplementation can reduce several MTX-associated adverse effects, particularly gastrointestinal symptoms, oral mucosal toxicity, and elevations in hepatic enzymes, without substantially compromising the therapeutic efficacy of low-dose MTX. In contrast, folinic acid (leucovorin) has a distinct role as rescue therapy following high-dose MTX treatment and in clinically significant MTX toxicity. Management of severe toxicity may also require hydration, urinary alkalinisation, monitoring of serum MTX concentrations and renal function, and, in selected cases, glucarpidase. Recent research has further explored oxidative stress, intestinal injury, and pharmacogenetic factors as potential contributors to MTX toxicity, although their clinical applications require further validation. Overall, appropriate folate

supplementation represents an important component of safe MTX therapy, while individualized monitoring and timely rescue remain essential for preventing and managing serious toxicity.

Keywords: Methotrexate, Folic Acid, Drug–Nutrient Interaction, Methotrexate Toxicity, Folate Supplementation.

1 INTRODUCTION

Methotrexate (MTX) is an important drug used in both oncology and the treatment of chronic inflammatory diseases.[1] It is widely used in conditions such as leukaemia, rheumatoid arthritis, and psoriasis. Although the dose and therapeutic goals differ across these conditions, MTX interferes with folate-dependent cellular pathways and thereby alters cellular proliferation and metabolism.[2] Folate, or vitamin B9, is required for several essential metabolic processes. It provides one-carbon units needed for the synthesis of purines and thymidylate and is therefore important for DNA synthesis and cell division.[3] Folate-dependent reactions also contribute to amino acid metabolism and cellular methylation processes. Tissues with rapid cell turnover, such as the bone marrow and gastrointestinal mucosa, are particularly dependent on an adequate supply of folate.[4]

The pharmacological actions of MTX are complex and depend on the dose and clinical setting. At higher doses, inhibition of dihydrofolate reductase (DHFR) is a major component of its antiproliferative action. MTX also undergoes intracellular polyglutamation, which prolongs its effects on several folate-dependent enzymes.[5] In low-dose therapy for inflammatory diseases, however, its anti-inflammatory effects involve additional pathways, including altered purine metabolism and increased adenosine signalling. The same effects that contribute to the therapeutic activity of MTX can also produce toxicity.[6] Gastrointestinal symptoms, oral mucositis, hepatotoxicity, and bone marrow suppression are among the important adverse effects associated with treatment. These effects have led to the widespread use of folate supplementation, particularly during long-term low-dose MTX therapy.[7] Understanding the interaction between MTX and folate is therefore important for reducing toxicity while maintaining the therapeutic benefits of treatment.

1.1 Mechanism of Methotrexate Action

Methotrexate (MTX) interferes with several folate-dependent metabolic pathways. One of its important targets is dihydrofolate reductase (DHFR), which converts dihydrofolate to tetrahydrofolate. Inhibition of DHFR reduces the availability of reduced folate cofactors required for nucleotide synthesis.[8] This can limit the formation of purines and thymidylate, thereby affecting DNA synthesis and cell proliferation. These effects are particularly important in cells undergoing rapid division. This explains the antiproliferative activity of MTX in many malignant conditions.[9] However, normal tissues with high rates of cell turnover can also be affected. The gastrointestinal mucosa and bone marrow are particularly susceptible, which contributes to adverse effects such as mucositis and myelosuppression. Thus, the clinical effects of MTX depend on the dose, treatment duration, intracellular metabolism, and disease being treated. The same pharmacological pathways that contribute to its therapeutic effects can also contribute to toxicity. This provides an important basis for understanding the role of folate supplementation during MTX therapy.

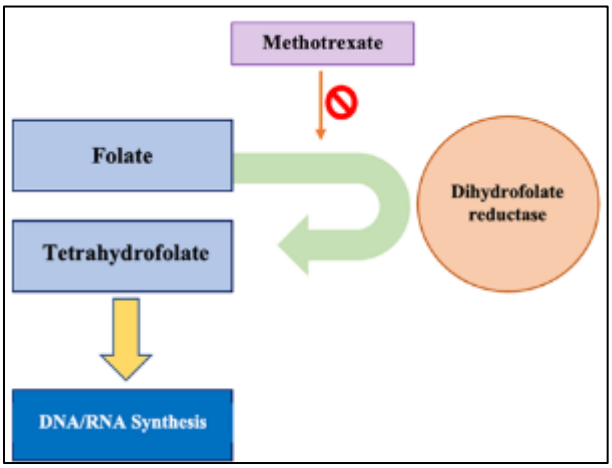

Figure 1: Illustration of mechanism of action of methotrexate.

1.2 Mechanism of Interaction with Folic Acid

Methotrexate (MTX) and folate have a close pharmacological relationship because MTX interferes with folate-dependent metabolic pathways. The nature of this interaction depends on the dose of MTX and the clinical setting.[10] In high-dose therapy, inhibition of dihydrofolate reductase (DHFR) reduces the availability of reduced folate cofactors and

contributes to the inhibition of nucleotide synthesis.[11] In low-dose therapy, additional mechanisms contribute to the anti-inflammatory effects of MTX. Folate supplementation can reduce some of the unwanted effects associated with low-dose MTX treatment.[12] Folic acid provides a source of folate that can support normal cellular metabolism. Clinical studies have shown that supplementation can reduce adverse effects, particularly gastrointestinal symptoms and abnormalities in liver enzymes, without causing a clinically important loss of MTX efficacy in most patients. This makes folic acid supplementation an important part of long-term low-dose MTX therapy.[13]

Folic acid and folinic acid should not, however, be considered equivalent. Folic acid requires conversion to reduced folate forms through normal folate metabolism. Folinic acid (leucovorin) is a reduced folate and can provide folate cofactors without requiring DHFR-mediated reduction.[14] It is therefore used as a rescue agent in selected clinical situations, particularly after high-dose MTX therapy and in significant MTX toxicity. The timing and dose of folate supplementation are important. Routine folic acid supplementation is generally used to improve the tolerability of low-dose MTX, whereas leucovorin is used when more immediate folate rescue is required.[15] These differences are important when considering the balance between reducing MTX toxicity and preserving its therapeutic effects

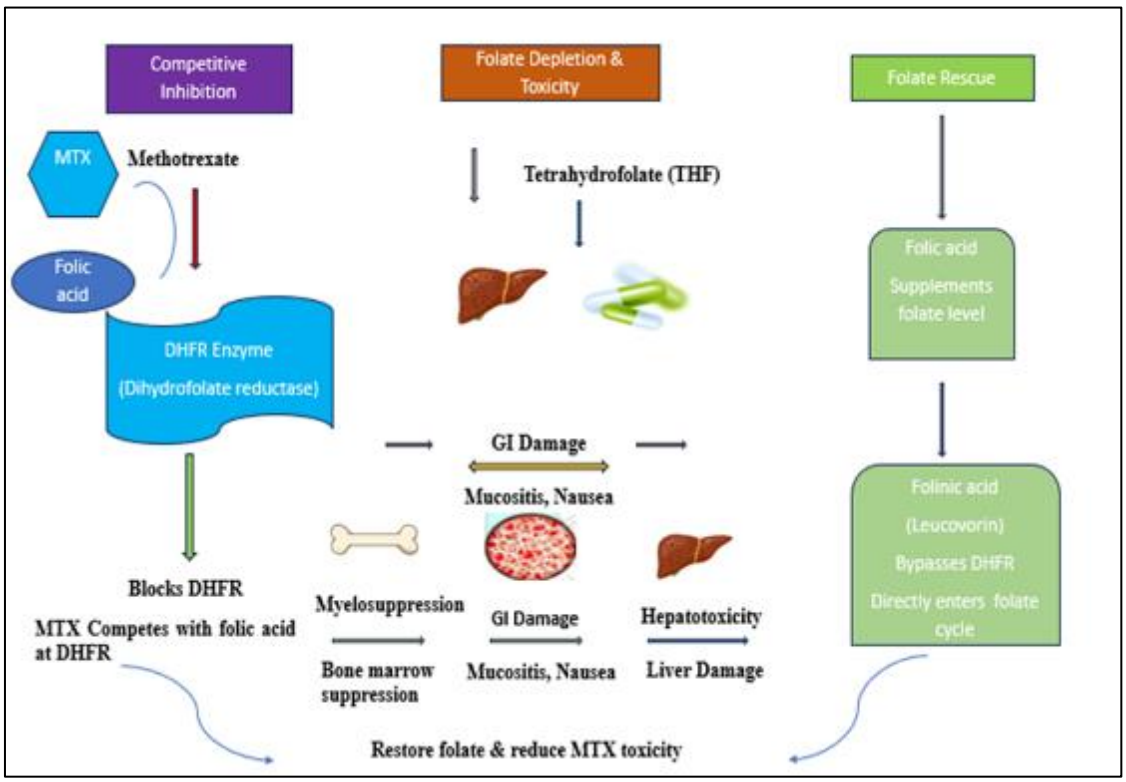

Figure 2: Mechanism of Interaction with Folic Acid & Methotrexate

2 CLINICAL MANIFESTATIONS OF THE INTERACTION

Methotrexate-related adverse effects can become more frequent or severe when folate supplementation is not provided during long-term low-dose therapy. The clinical presentation varies with the dose, treatment duration, renal function, and other patient-related factors. Gastrointestinal and mucosal effects are among the commonly reported problems.[16] Patients may develop nausea, reduced appetite, abdominal discomfort, or oral mucositis. Painful oral ulcers can sometimes interfere with eating and may lead to poor treatment adherence. Hepatic effects are also important during long-term treatment.[17] Methotrexate may cause elevations in liver transaminases, although the severity varies between patients. Regular monitoring of liver function is therefore important during therapy. Bone marrow toxicity is less common but can be serious. Myelosuppression may result in anaemia, leukopenia, or thrombocytopenia.[18] Severe cases can increase the risk of infection or bleeding and may require interruption of methotrexate treatment and appropriate rescue measures.[19] These adverse effects can affect treatment adherence, particularly when gastrointestinal or mucosal symptoms persist. Folate supplementation has therefore become an important strategy for improving the tolerability of low-dose methotrexate therapy. However, folate supplementation does not replace routine clinical and laboratory monitoring for methotrexate toxicity.

3 ROLE OF FOLIC ACID SUPPLEMENTATION

Folic acid supplementation is widely used with low-dose methotrexate (MTX), particularly in rheumatoid arthritis and other chronic inflammatory diseases. MTX interferes with folate-dependent pathways, which may contribute to some of its adverse effects.[20] Folate supplementation can help improve the tolerability of treatment without causing a clinically important reduction in MTX efficacy in most patients. Clinical studies have reported fewer adverse effects among patients receiving folic acid with MTX. The benefits are particularly evident for gastrointestinal symptoms and abnormalities in liver enzymes. Nausea, reduced appetite, and oral discomfort may become less troublesome with supplementation.[21] This can make long-term MTX treatment easier for patients to tolerate. Folic acid supplementation may also reduce MTX-associated elevations in liver transaminases. This is clinically relevant because hepatic adverse effects can lead to additional monitoring, dose adjustment, or treatment interruption. By reducing treatment-related toxicity, folate supplementation may also improve adherence to MTX therapy.

Evidence from systematic reviews supports the use of folic acid as a strategy to reduce several MTX-related adverse effects. A reduction in gastrointestinal symptoms, abnormal liver enzyme levels, and treatment withdrawal has been reported in patients receiving folate supplementation.[22] However, the magnitude of benefit varies between studies and may depend on the dose and timing of folic acid administration. Importantly, folic acid supplementation should be viewed as a supportive measure rather than a substitute for appropriate MTX monitoring. Patients receiving MTX still require appropriate assessment of blood counts, liver function, renal function, and other clinical risk factors.[23] The available evidence supports folic acid supplementation as an effective approach to improve the safety and tolerability of long-term low-dose MTX therapy

4 EFFECT ON METHOTREXATE EFFICACY

One important concern with folic acid supplementation is whether it may reduce the therapeutic effect of methotrexate (MTX). This question is particularly relevant in patients receiving long-term low-dose MTX for inflammatory diseases. A recent systematic review of methotrexate-associated hepatotoxicity in patients with psoriasis highlighted that hepatic toxicity is multifactorial and influenced by patient-specific factors such as obesity, diabetes, hyperlipidaemia, alcohol consumption, and pre-existing liver disease. The review also noted that folic acid supplementation may help mitigate MTX-associated hepatic toxicity, although the optimal supplementation regimen remains inconsistent across clinical practice.[24] However, most of the available evidence relates to low-dose MTX used in inflammatory diseases. These findings should therefore not be directly extrapolated to high-dose MTX regimens used in oncology, where folate rescue follows a different clinical strategy.

Table 1: Difference between Folic Acid vs Folinic Acid

Feature	Folic acid	Folinic acid (leucovorin)
Chemical form	Oxidized folate	Reduced folate
DHFR requirement	Yes, for conversion to reduced folate	Bypasses DHFR
Typical role	Supplementation with low-dose MTX	Rescue therapy
Low-dose MTX toxicity	May help prevent toxicity	Used when clinically significant toxicity occurs
High-dose MTX	Not the standard rescue agent	Standard rescue strategy
Timing	Depends on regimen	Carefully timed according to MTX regimen/levels
Therapeutic drug monitoring	Usually not required	Essential in HD-MTX rescue protocols
Glucarpidase	Not required	May be used alongside leucovorin in selected severe delayed-clearance cases

5 ROLE OF FOLINIC ACID (LEUCOVORIN) IN METHOTREXATE THERAPY

Folinic acid, also known as leucovorin, is a reduced form of folate used in specific situations during methotrexate (MTX) treatment. Its role is different from that of routine folic acid supplementation. Folinic acid can provide reduced folate cofactors without depending on dihydrofolate reductase (DHFR) for their formation.[25] Leucovorin is an important

component of rescue therapy following high-dose methotrexate (HD-MTX). It is usually started at a planned time after MTX administration and continued according to the treatment protocol and, where appropriate, serum MTX concentrations.[26] The aim is to protect normal tissues from prolonged folate antagonism while allowing the intended antitumor effect of MTX to occur.

Leucovorin is also used in the management of significant MTX toxicity. This is particularly important when MTX elimination is delayed and drug concentrations remain elevated. Renal impairment is an important cause of delayed MTX clearance. Early recognition and timely leucovorin administration are therefore essential in severe toxicity. Management of serious MTX toxicity may also require supportive measures such as adequate hydration, urinary alkalinization, and close monitoring of renal function and serum MTX concentrations. In selected cases of severe toxicity with delayed MTX clearance, glucarpidase may be considered.[27] Thus, leucovorin should be viewed as part of a broader toxicity-management strategy rather than as a replacement for appropriate monitoring and supportive care.

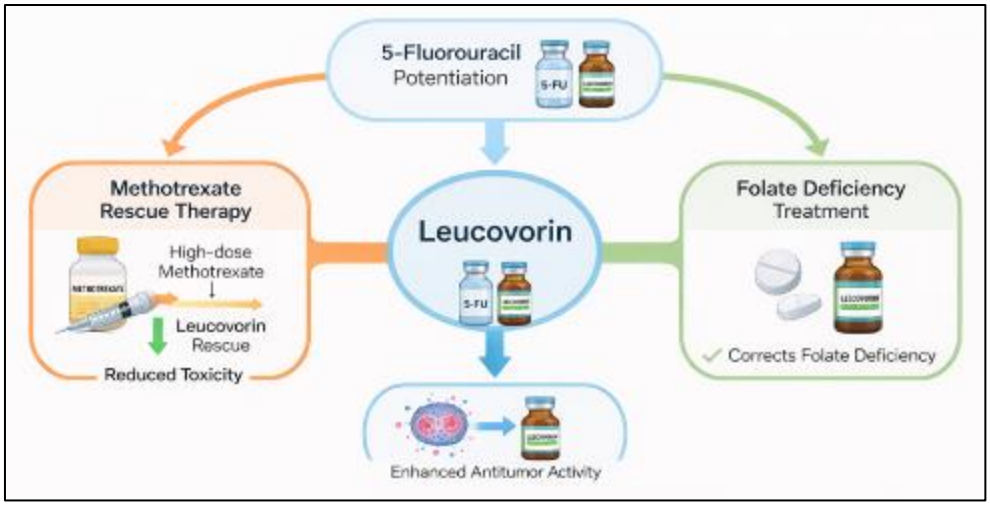

Figure 3: Role of Folinic Acid (Leucovorin) in Methotrexate Therapy

6 RECENT ADVANCES

Individualized approaches to folate supplementation have also received attention. Factors such as MTX dose, treatment duration, renal function, nutritional status, and previous toxicity may influence the risk of adverse effects. Genetic variants in folate-related pathways, including **MTHFR**, have been studied as possible predictors of MTX response and toxicity. Advances in the management of MTX toxicity have focused mainly on early recognition and timely rescue.[28] Glucarpidase is an important option for selected patients with severe MTX toxicity and delayed clearance. It rapidly converts MTX into inactive metabolites and can markedly reduce circulating MTX concentrations. Its use is generally considered alongside leucovorin and supportive treatment rather than as a replacement for them.[29] Current management of significant MTX toxicity therefore relies on a combination of appropriate hydration, urinary alkalinization, monitoring of renal function and serum MTX concentrations, and timely leucovorin rescue.[19] Early recognition of delayed clearance remains essential for preventing serious complications.

Clinical Guidelines and Recommendations

The dose and timing of supplementation may vary according to clinical guidelines, treatment indication, methotrexate dose, and individual patient factors. Commonly used regimens include folic acid 1 mg once daily, with some treatment protocols omitting folic acid on the day of methotrexate administration.[13] Another widely used approach is weekly supplementation, in which folic acid is administered as a single dose approximately 24–48 hours after methotrexate.[30] The choice between daily and weekly supplementation depends on local clinical practice and patient-specific requirements.

6.1 Clinical Benefits

The principal clinical benefit of folic acid supplementation is the reduction of methotrexate-associated toxicity and improvement in treatment tolerability. Reduction in these adverse effects may improve patient comfort, reduce treatment interruptions, and support adherence to long-term methotrexate therapy.[31] Thus, folic acid provides a practical approach to improving the safety profile and long-term acceptability of methotrexate therapy while allowing patients to continue receiving its therapeutic benefits.

7 DISCUSSION

Methotrexate (MTX) continues to have an important place in the treatment of malignancies and chronic inflammatory disorders. Its therapeutic and toxic effects are closely linked to its interference with folate-dependent pathways, although the underlying mechanisms differ according to dose and clinical indication. In high-dose therapy, inhibition of dihydrofolate reductase and intracellular retention of MTX polyglutamates contribute to impaired nucleotide synthesis and injury to rapidly dividing normal tissues. In contrast, the anti-inflammatory effects of low-dose MTX involve additional mechanisms, particularly alterations in purine metabolism and adenosine signaling. This difference is important when interpreting the role of folate supplementation across different treatment settings.

A clear distinction should also be maintained between folic acid supplementation and folinic acid rescue. Folic acid is generally used during low-dose MTX therapy to reduce treatment-related toxicity, whereas folinic acid (leucovorin) has a more specific role in high-dose MTX rescue and significant toxicity. Patients with delayed MTX elimination, particularly those with impaired renal function, require prompt assessment and appropriate management.[32] Monitoring serum MTX concentrations and renal function, together with adequate hydration and urinary alkalinization, is central to the management of high-dose MTX exposure. In selected cases of delayed clearance with severe toxicity, glucarpidase may be required in addition to leucovorin and supportive treatment. The possibility of tailoring MTX therapy according to individual risk is an emerging area of interest. Factors such as renal function, comorbidities, concomitant medicines, treatment intensity, and previous toxicity can influence patient susceptibility. Genetic variations in folate-related pathways, including MTHFR, have also been investigated; however, current evidence is insufficient to support routine genotype-guided adjustment of MTX or folate supplementation.[33] Future research should therefore focus on identifying reliable predictors of toxicity and determining whether individualized supplementation and monitoring strategies can further improve the safety and long-term use of MTX.

8 CONCLUSION

The review also highlights the important distinction between routine folic acid supplementation and folinic acid rescue. Folic acid is mainly used to reduce toxicity during low-dose methotrexate therapy, whereas folinic acid has a specific role in high-dose methotrexate rescue and the management of clinically significant toxicity. In patients with delayed methotrexate elimination, particularly those with renal impairment, timely recognition and appropriate management are essential. Leucovorin, supportive measures, therapeutic monitoring, and, in selected severe cases, glucarpidase may be required. Thus, effective management of methotrexate toxicity involves a coordinated approach rather than reliance on folate supplementation alone.

Limitations

This review has several limitations. The available evidence includes studies conducted in different clinical populations, using different methotrexate doses, folate regimens, treatment durations, and outcome measures, which makes direct comparison between studies difficult. Much of the evidence supporting routine folic acid supplementation comes from patients receiving low-dose methotrexate for inflammatory diseases and therefore cannot automatically be extrapolated to high-dose methotrexate used in oncology. In addition, some emerging evidence concerning oxidative stress, intestinal injury, and pharmacogenetic factors is derived predominantly from experimental or observational research, and its clinical relevance remains uncertain. Variation in recommendations regarding the dose and timing of folate supplementation also limits the ability to identify a single universally applicable regimen.

Future Perspectives

Future research should focus on developing more individualized approaches to folate supplementation based on methotrexate dose, renal function, treatment duration, comorbidities, and individual risk of toxicity. Further clinical studies are also needed to clarify the optimal dose and timing of folic acid and to determine whether emerging biomarkers or pharmacogenetic factors can reliably predict methotrexate toxicity. Greater understanding of oxidative stress, intestinal injury, and other cellular mechanisms may provide additional opportunities for preventing or treating methotrexate-associated toxicity. Such advances could help achieve a more personalized balance between maintaining the therapeutic benefits of methotrexate and minimizing its adverse effects.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

No conflicts of interest regarding this manuscript.

REFERENCES

[1] Koźmiński P, Halik PK, Chesori R, Gniazdowska E. Overview of dual-acting drug methotrexate in different neurological diseases, autoimmune pathologies and cancers. Int. J. Mol. Sci.2020;21(10).

[2] Udawant S, Zilate S. Therapeutic Role of Methotrexate in Effective Treatment of Psoriasis: A Review. J Res Med Dent Sci [Internet] 2022;10(8):25. Available from: www.jrmds.in

[3] Zheng Y, Cantley LC. Toward a better understanding of folate metabolism in health and disease. J Exp Med 2019;216(2):253–66.

[4] Bailey LB, Stover PJ, McNulty H, Fenech MF, Gregory JF, Mills JL, et al. Biomarkers of nutrition for development-Folate review. J Nutr 2015;145(7):1636S-1680S.

[5] Bedoui Y, Guillot X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, et al. Methotrexate an old drug with new tricks. Int J Mol Sci 2019;20(20).

[6] Duff Putu, Jean Shoveller., Julio Montaner., Cindy Feng., Rachel Nicoletti., Kate Shannon . GO, Woalder. Adenosine and Adenosine Receptors in the Pathogenesis and Treatment of Rheumatic Diseases. Physiol Behav 2017;176(1):139–48.

[7] Peixoto AC, de Almeida Mota R, Rodrigues ALM, Paraiso MM, Cardoso LA, Almeida J. A Clinical Case of Methotrexate Toxicity. J Med Cases [Internet] 2025;16(8):314–7. Available from: https://www.doi.org/10.14740/jmc5159

[8] Hess JA, Khasawneh MK. Cancer metabolism and oxidative stress: Insights into carcinogenesis and chemotherapy via the non-dihydrofolate reductase effects of methotrexate. BBA Clin [Internet] 2015;3:152–61. Available from: http://dx.doi.org/10.1016/j.bbacli.2015.01.006

[9] Kakkadath M, Naidu D, Kanthlal SK, Sharun K. Combating Methotrexate Resistance in Cancer Treatment: A Review on Navigating Pathways and Enhancing Its Efficacy With Fat-Soluble Vitamins. Scientifica (Cairo) 2025;2025(1).

[10] Muller IB, Lin M, Jonge R de, Will N, López-Navarro B, Laken C van der, et al. Methotrexate Provokes Disparate Folate Metabolism Gene Expression and Alternative Splicing in Ex Vivo Monocytes and GM-CSF- and M-CSF-Polarized Macrophages. Int J Mol Sci 2023;24(11).

[11] Hsieh YC, Tedeschi P, Lawal RAB, Banerjee D, Scotto K, Kerrigan JE, et al. Enhanced degradation of dihydrofolate reductase through inhibition of NAD kinase by nicotinamide analogs. Mol Pharmacol 2013;83(2):339–53.

[12] Shea, Swinden, Ghogomu T, Ortiz, Wells. Shea B, Swinden MV, Tanjong Ghogomu E, Ortiz Z, Katchamart W, Rader T, Bombardier C, Wells GA, Tugwell P. Cochrane Libr 2023;2(1):1–8.

[13] Bishnoi P, Kumari R, Thappa DM. Monitoring methotrexate hepatotoxicity in psoriasis. Indian J Dermatol Venereol Leprol 2011;77(5):545–8.

[14] Menezo Y, Elder K, Clement A, Clement P. Folic Acid, Folinic Acid, 5 Methyl TetraHydroFolate Supplementation for Mutations That Affect Epigenesis through the Folate and One-Carbon Cycles. Biomolecules 2022;12(2).

[15] Hamed KM, Dighriri IM, Baomar AF, Alharthy BT, Alenazi FE, Alali GH, et al. Overview of Methotrexate Toxicity: A Comprehensive Literature Review. Cureus 2022;14(9).

[16] Berkun Y, Levartovsky D, Rubinow A, Orbach H, Aamar S, Grenader T, et al. Methotrexate related adverse effects in patients with rheumatoid arthritis are associated with the A1298C polymorphism of the MTHFR gene. Ann Rheum Dis 2004;63(10):1227–31.

[17] Shrestha R, Ojha SK, Jha SK, Jasraj R, Fauzdar A. Methotrexate-Induced Mucositis: A Consequence of Medication Error in a Rheumatoid Arthritis Patient. Cureus 2023;15(9):4–11.

[18] Jankowski J, Kotyla P. Methotrexate – adverse effects and special clinical situations. Rheumatol Forum 2026;12(0):1–5.

[19] Howard SC, McCormick J, Pui CH, Buddington RK, Harvey RD. Preventing and Managing Toxicities of High-Dose Methotrexate. Oncologist 2016;21(12):1471–82.

[20] Jara-Palacios MA, Chun W, Traub NL. Potential contributors to low dose methotrexate toxicity in a patient with rheumatoid arthritis and pernicious anemia: case report. BMC Rheumatol 2021;5(1):4–9.

[21] Waage et al. Adverse Effects of Low-Dose Methotrexate. Physiol Behav 2017;176(1):139–48.

[22] Molaqanbari MR, Zarringol S, Talari HR, Taghizadeh M, Bahmani F, Mohtashamian A, et al. Effects of Folic Acid Supplementation on Liver Enzymes, Lipid Profile, and Insulin Resistance in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial. Adv Biomed Res 2023;12(1):1–10.

[23] Dhillon GS, Chauhan S, Jalal Y, Ghobrial Y, Ahmed B. Low-Dose Methotrexate Toxicity Presenting as Pancytopenia. Cureus 2022;14(12):10–4.

[24] Boehncke WH, Constantin MM, Carrascosa-Carrillo JM, Rakvit P, Varlet AA, Clanche SLE, et al. A Systematic Literature Review on Methotrexate Hepatotoxicity in Psoriasis Management: Preconceived Notion or Real Threat? Acta Derm Venereol 2026;106:1–13.

[25] Budak MŞ, Oğlak SC, Akgöl S, Can B, Arkan K, Erkmen AD, et al. Folic acid versus folinic acid during methotrexate treatment for low-risk gestational trophoblastic neoplasia. Ginekol Pol 2025;96(3):200–5.

[26] Barreto JN, Peterson KT, Barreto EF, Mara KC, Dierkhising RA, Leung N, et al. Early, empiric high-dose leucovorin rescue in lymphoma patients treated with sequential doses of high-dose methotrexate. Support Care Cancer 2021;29(9):5293–301.

[27] Ramsey LB, Balis FM, O'Brien MM, Schmiegelow K, Pauley JL, Bleyer A, et al. Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance. Oncologist 2018;23(1):52–61.

[28] Xu M, Wu S, Wang Y, Zhao Y, Wang X, Wei C, et al. Association between high-dose methotrexate-induced toxicity and polymorphisms within methotrexate pathway genes in acute lymphoblastic leukemia. Front Pharmacol 2022;13(November):1–11.

[29] Widemann BC, Balis FM, Kim AR, Boron M, Jayaprakash N, Shalabi A, et al. Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: Clinical and pharmacologic factors affecting outcome. J Clin Oncol 2010;28(25):3979–86.

[30] Dhir V, Sandhu A, Kaur J, Pinto B, Kumar P, Kaur P, et al. Comparison of two different folic acid doses with methotrexate - A randomized controlled trial (FOLVARI Study). Arthritis Res Ther [Internet] 2015;17(1):1–9. Available from: http://dx.doi.org/10.1186/s13075-015-0668-4

[31] Omran ME, Saleem RI, Omran DE, Hadi AA, Jubair KS, Jassim ZS, et al. Adherence to folic acid among methotrexate-treated patients with rheumatologic diseases: a cross-sectional study. Rom J Rheumatol 2025;34(2):92–9.

[32] Gros L, Roldán A, Cabero-Martínez A, Domínguez-Pinilla N, de la Fuente A, González-Barca E, et al. Incidence and management of patients with methotrexate delayed elimination in the clinical practice: A Delphi study. J Oncol Pharm Pract 2023;29(4):794–801.

[33] Ledowsky CJ, Schloss J, Steel A. Variations in folate prescriptions for patients with the MTHFR genetic polymorphisms: A case series study. Explor Res Clin Soc Pharm [Internet] 2023;10(April):100277. Available from: https://doi.org/10.1016/j.rcsop.2023.100277