СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted[1] **ISSN Online 2406-0895**

Review Article / Прегледни рад

Dušica J. Popović[1,2], Jovan K. Popović[2,3,*], Kosta J. Popović[2]

New promising repurposed drugs and vaccines anticancer treatment possibilities – review of the current reports

Нове обећавајуће антиканцерске терапије пренамењеним лековима и вакцинама – преглед најновијих истраживања

[1]State University of Novi Pazar, Novi Pazar, Serbia;
[2]University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia;
[3]Serbian Medical Society, Academy of Medical Sciences of the Serbian Medical Society, Belgrade, Serbia

Received: November 16, 2025
Revised: December 26, 2025
Accepted: January 21, 2026
Online First: February 10, 2026
DOI: https://doi.org/10.2298/SARH251116014P

[1]**Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

***Correspondence to:**
Jovan K. POPOVIĆ
Academy of Medical Sciences of the Serbian Medical Society, 19 George Washington Str., Belgrade 11000, Serbia;
University of Novi Sad, Faculty of Medicine, Department of Pharmacology, Toxicology and Clinical Pharmacology, 3 Hajduk Veljkova Str., Novi Sad 21000, Serbia
E-mail: **jovapopmf@gmail.com; jovan.popovic@mf.uns.ac.rs**

New promising repurposed drugs and vaccines anticancer treatment possibilities – review of the current reports

Нове обећавајуће антиканцерске терапије пренамењеним лековима и вакцинама – преглед најновијих истраживања

SUMMARY
The potential of repurposing already approved, registered non-oncological drugs and vaccines for the development of new anticancer treatments is presented. A large number of registered non-oncological drugs and vaccines modulate key cancer-related processes (such as neoangiogenesis, apoptosis, necroptosis, ferroptosis, autophagy, and aerobic glycolysis) by targeting the same, upstream or downstream molecular biomarkers and signaling pathways, in the same anticancer direction. Beyond individual agents, combinations of repurposed drugs and vaccines are of greater interest for investigation, as they may reveal synergistic anticancer effects. Some repurposed drugs and vaccines are outlined for less toxic, more efficient, and affordable cancer therapies, with potential for further clinical investigations and possible impact on official clinical treatment guidelines. This review aims to present the current reports of drugs and vaccines repurposed in the anticancer treatment.
Keywords: cancer treatment; repurposed drugs; vaccines

САЖЕТАК
Приказује се потенцијал пренамењених већ одобрених и регистрованих неонколошких лекова и вакцина за развој нових антиканцерских терапија. Велики број регистрованих неонколошких лекова и вакцина модулише кључне процесе повезане са канцером (као што су неоангиогенеза, апоптоза, некроптоза, фероптоза, аутофагија и аеробна гликолиза), делујући на исте усходне или нисходне молекуларне мете, биомаркере и сигналне путеве, у истом антиканцерском правцу. Осим појединачних, за испитивање су много интересантније комбинације пренамењених лекова и вакцина где може бити откривено синергистичко антиканцерско деловање. Неки пренамењени лекови и вакцине се истичу као потенцијални кандидати за мање токсичне, ефикасније и приступачније терапије канцера, са потенцијалом за даља клиничка истраживања и могућим утицајем на званичне клиничке смернице лечења. Овај преглед има за циљ да представи резултате најновијих истраживања неонколошких лекова и вакцина пренамењених за лечење канцера.
Кључне речи: антиканцерска терапија; пренамењени лекови; вакцине

INTRODUCTION

The standard oncological treatment regimen, as defined in the regularly updated Clinical Practice Guidelines and implemented globally, typically includes surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy, immunotherapy, photodynamic and laser therapy, cryotherapy, thermal therapy, stem cell therapy, and nanomedicine-based therapies. Cancer management involves expert diagnosis, treatment planning, symptom management, supportive care, and addressing complications related to cancer or its treatments, such as those arising during radiotherapy or chemotherapy. Drugs and vaccines repurposing in cancer treatment explores the potential of previously approved, affordable, and less toxic or expensive pharmaceuticals as new weapons in the fight against cancer [1, 2].

DRUG REPURPOSING

A large number of the aforementioned registered non-oncological drugs modulate key cancer-associated processes (proliferation, neoangiogenesis, aerobic glycolysis, multidrug resistance, apoptosis, necroptosis, pyroptosis, ferroptosis, autophagy), by acting in the same anticancer direction on overlapping molecular targets / biomarkers, such as (abbreviations used: tumor promoter (P), tumor suppressor (S); effects on other targets: stimulation /, inhibition \):

1) Transcription factors: NF-κB a (P - tumor promoter), p65 (Rel A) (P), Integrins (P), STATs (P), Nrf2 (S - tumor suppressor), Nanog (P), KLF4 (P), Sox2 (P), Oct4 (P), JNKs (P), HES1, K13, MUC2 (P), VDR - vitamin D receptor (S), Hippo \ YAP (P), TCFs (P), LEFs (P);

2) Cell cycle proteins: Cyclin D_1 (P), CDKs (P), p21 (S), p27 (S), Ki-67 (P), PCNA (P), Akt = PKB (P), mTOR (P), EGFR (P), Raf (P), RAS (P), MAPK (P), PI3K (P);

3) Cell signaling cascades proteins: MDR (MDPRs, MRP1-7, P-gp tyrosine kinase) (P), IκB (P), Hedgehog (P), ABC (P), PKC (P, S), JAKs (P), Wnt / β-catenin (P), ILs (IL1, IL6, IL8, IL10, IL17) (P), IGF-1 (P), PTEN (S), Eps8 (P);

4) Apoptosis and/or necroptosis associated proteins: Bcl-2 (P), Bax (S), Cytochrome C (S), PARPs (P), p53 (S), p63 (S), p73 (P, S), caspase 3, 8, 9, 12 (S), p38MAPK (P), Mcl-1 (P);

5) Death receptors on the cell surface: FAS (S), TRAIL (P, S);

6) Autophagy (ATG) related proteins: ATG (ATG5, ATG9A, ATG12, ATG13) (P, S), LC3 (S), Beclin1 (P, S), p62 (P), PAK1 (P);

7) Antioxidant defense proteins and other targets / markers: ROS (P, S), COX-2 (PTG S2) (P), iNOS / NO (P), TNF-α (P), PGE2 (P);

8) Angiogenesis and tumor microenvironment associated proteins: CD31 (= PECAM1) (P), CD34 (P), HIFs (HIF-1α, HIF-1β, HIF-2α, HIF-2β) (P), VEGF / VEGFR (P), MEK / ERK (P), CXC (P), CXCL12 (= SDF1) (P), CXCR4 (P), FAK (= PTK2) (P);

9) Cellular metabolism and metabolic reprogramming associated proteins: GLUTs (1-13) (P), TLRs (1-24) (P);

10) Embryonic development associated proteins: TGF-β / SMAD (P);

11) Membrane receptors: PANX1 (P), P2X4 (P), P2X7 (P);

12) Membrane bound proteins (transcription factors) shuttling between the cytoplasm and nucleus: Notch (P);

13) Oncogen addiction targets: PTK (P), MYC (C-, N-, L-) (P), cABL (P).

Also, the aforementioned drugs modulate various signaling pathways, in the same anticancer direction. A significant proportion of anticancer signaling pathways are functionally linked to NF-κB signaling, either upstream, downstream, or directly [3] (symbols used for effects on other targets: stimulation /, inhibition \): IκB (IKK)/NF-κB/STAT3\apoptosis; EGFR/RAS/Raf/p38/MAPK/MEK/ERK/Akt/mTOR/NF-κB/P-gp (MDPR); PI3K/Akt/JNK/IκBα/NF-κB/P-gp; TGF-α/PI3K/Akt/mTOR/HIF/IκBα/NF-κB/HIF/VEGF; PI3K/PKC/NF-κB…; STAT3/PI3K/Akt /…/NF-κB…; p38/MAPK/PI3K/Akt/…/NF-κB …; p38/MAPK/JNK/ERK/Akt/IκBα/NF-κB…; TNF/IκB (IKKα, IKKβ, IKKγ = NEMO)/NF-κB…; IL1/IκB/NF-κB…; TLRs/IκB/NF-κB…; TLRs/IL1/IκB/NF-κB…; TLR4/TNF-α, IL1β/IκB/NF-κB…;TLRs/p38/MAPK/PI3K/Akt/…/NF-κB…; TLRs/p38/MAPK/ERK/Akt/IκBα/NF-κB…; PANX1/ILs/NF-κB…; P2X4, P2X7/ROS/…/NF-κB. Non-oncological agents such as mebendazole, deoxycholic acid, and folinic acid stimulate the NF-κB, a key cellular signaling pathway that promotes cell survival and proliferation while inhibiting apoptosis, thereby fostering pro-tumorigenic processes.

Combining chemically distinct non-oncologic agents targeting the same anticancer pathways can enhance efficacy without increasing toxicity, potentially offering synergistic anticancer regimens. The overlap in anticancer targets justifies parallel rescue and dose–response experiments.

Among antidiabetic medications, metformin may demonstrate anticancer properties, potentially inhibiting cancer cell proliferation, promoting apoptosis, and increasing cancer cell sensitivity to chemotherapy. Further studies are crucial to clarify the mechanisms of anticancer effects and assess the clinical efficacy and safety of antidiabetic drugs [4].

Our experimental findings *in vivo* demonstrated that metformin administered alone [5], or in combination with one of the following agents: caffeine [6], disulfiram [7, 8], nitroglycerin [9, 10, 11], itraconazole [10, 11], or diclofenac [11, 12] exerted significant anticancer effects against fibrosarcoma in hamsters, without inducing observable toxicity. Importantly, the administered doses were equivalent to standard therapeutic doses used in humans. Anticancer effects of examined dual drug combinations were validated through dose-response experiments and synergism was determined by Combination Index (CI) analysis (CI < 1). The hypothesis that the examined combinations act synergistically against cancer cells through NF-κB inhibition was successfully tested in rescue experiments by adding an NF-κB stimulator, such as mebendazole or deoxycholic acid, to these combinations in order to abrogate the anticancer effects and 'rescue' tumor growth. Therefore, the use of metformin in combination with caffeine,

disulfiram, nitroglycerin, itraconazole, or diclofenac may represent a promising and safe adjuvant anticancer approach, warranting further clinical investigation [6-12]. We anticipate that the therapeutic efficacy of metformin, when combined with anticancer therapies, will exceed these anticancer therapies without metformin. It is our expectation that such strategies will provide a more effective and safer treatment approach in clinical practice, while also guiding future research into the potential of metformin in cancer therapy [13].

In a clinical study of patients with advanced cervical cancer using fluoroazomycin arabinoside, metformin decreased tumor hypoxia and improved cervical cancer response to radiation [14].

An *in vitro* investigation on repurposed pharmacological agents revealed that the combination of disulfiram and copper gluconate displayed a marked cytotoxic effect against glioblastoma stem cells [15].

A recent *in vitro* study repositioned propranolol, a non-selective beta-blocker commonly used in the treatment of various cardiovascular conditions, as a promising and cost-effective therapeutic option for colorectal cancer treatment, identifying T-cells as its primary target [16]. Oral administration of propranolol has been shown to delay tumor progression and improve survival rate of tumor-bearing mice in fibrosarcoma and colon cancer models. Propranolol inhibited tumor angiogenesis and promoted T cell infiltration. Recent study identified propranolol as an immunomodulatory agent, suggesting its potential to enhance immunotherapies with checkpoint inhibitors in patients with soft tissue sarcoma, and possibly in other cancer types [17].

An *in vitro* study demonstrated that propranolol (non-selective β1/2- adrenergic receptor blocker) and selective β2-adrenergic receptor blockers induced apoptosis in human colorectal carcinoma HCT116 cells following radiation treatment. Furthermore, β2-adrenergic receptor blockade markedly inhibited tumor growth *in vivo* in nude mice bearing HCT116 colorectal cancer xenografts, suggesting its potential use as an adjuvant strategy to enhance clinical outcomes of colorectal cancer after radiotherapy [18].

A recently identified novel class of ciprofloxacin-amino acid conjugates has demonstrated significant potency against human breast, colon, and lung cancer cell lines. These results indicate that the proper modification of ciprofloxacin could lead to the development of promising anticancer agents through appropriate derivatization in easy synthetic processes [19].

Itraconazole demonstrated promising properties as anticancer agent and may be a potent adjuvant to immunotherapy for endometrial cancer [20]. Antifungal drug itraconazole *in vitro* effectively inhibited the proliferation and invasion of Ishikawa cells by inducing apoptosis. *In vivo* experiments on tumor-bearing mice further confirmed its synergistic potential in

combination with immune checkpoint inhibitors: tumor volume and weight were significantly reduced [20].

A recent study highlighted the anticancer effects of antihistaminic drug loratadine on lung adenocarcinoma cells, both *in vitro* and *in vivo*. Loratadine inhibited cell proliferation, increased autophagy and apoptotic cell death. In the mouse model, loratadine reduced tumor growth and angiogenesis, while promoting autophagy and apoptosis. These findings suggest that loratadine may serve as a potential therapeutic agent for inhibiting lung adenocarcinoma progression, warranting further investigation [21]. A retrospective study involving 4,522 patients suffering from lung cancer in period 2006 - 2018 demonstrated a positive correlation between loratadine administration and improved survival outcomes, with a dose-dependent effect. Higher loratadine uptake was linked to better survival rates in lung cancer patients. Additionally, lung cancer mortality showed a dose-dependent reduction as the cumulative use of loratadine increased [22].

The results of a seven-year retrospective study that included 734 patients with immunogenic tumors revealed that patients treated with cationic amphiphilic antihistamines desloratadine, cyproheptadine, and ebastine exhibited significantly improved median overall survival and progression-free survival, along with a nearly 50% reduction in the risk of all-cause mortality [23].

A retrospective analysis demonstrated that melanoma and lung cancer patients who received H1-antihistamines during immunotherapy treatment showed significantly better clinical outcomes, including improved survival rates. These results strongly suggest the potential benefit of using antihistamines in cancer patients with allergies and elevated plasma histamine levels [24].

An *in vitro* study conducted on HeLa cells revealed novel mechanisms of action for azelastine hydrochloride, a drug commonly used in antiallergic treatment. The results highlighted the antiproliferative, cytotoxic, autophagic, and apoptotic effects of azelastine on HeLa cells, suggesting its potential for future application in cancer therapy [25].

A recent *in vitro* study demonstrated that acetylsalicylic acid produced apoptosis in human colon cancer cell line HT29 in a manner that is dependent on its concentration [26].

A three-year, double-blind, randomized, placebo-controlled trial was conducted with patients diagnosed with rectal and colon cancer. A total of 314 patients were administered acetylsalicylic acid, while 312 received a placebo. The results indicated that acetylsalicylic acid significantly reduced the incidence of cancer recurrence compared to the placebo group [27].

Dysregulation of estrogen receptor alpha, found in about 70% of breast cancers, is key to the disease initiation and progression. Recent *in vitro* study suggests that acetylsalicylic acid may be a potential therapeutic agent for targeting estrogen receptor alpha, particularly in breast cancers resistant to tamoxifen [28].

The cytotoxic effects of the novel nano Chitosan-Paracetamol composite were evaluated using the human colon cancer cell line HCT-29. The findings highlighted the potent biological activity of the nano composite, effectively inhibiting the proliferation of colon cancer cells [29].

Recent *in vitro* and *in vivo* studies on mouse models of adenocarcinoma, hepatocellular carcinoma, and breast cancer revealed that high doses of vitamin C (ascorbic acid), when combined with oncolytic adenoviruses, produced notable synergistic antitumor effects, including a significant increase in the number of T cells [30].

Experiments *in vitro* on renal carcinoma cell lines and *in vivo* on mouse xenograft model demonstrated that vitamin C treatment enhanced the efficacy of immunotherapy and significantly increased the intratumoral infiltration of T cells, suggesting a potential role of vitamin C in anticancer therapy [31].

The combination of vitamin D and sericin demonstrated significant anticancer effects at low doses against human non-small cell lung cancer cells. *In vitro* findings revealed a strong correlation with *in silico* analyses, highlighting a significant enhancement of apoptosis in lung cancer cells [32].

A recent study demonstrated that magnetothermodynamic therapy, utilizing a novel vitamin K3 nanoparticle complex with copper, zinc, and ferrite, exhibited anticancer effects both *in vitro* and *in vivo* against lung adenocarcinoma. Complete tumor elimination was achieved *in vivo* within 30 days [33]. The synergistic therapy based on vitamin K3 nanoparticles showed significant anticancer effects by inducing apoptosis, causing tumor regression *via* reactive oxygen species (ROS) generation, inhibiting cell proliferation, and reducing metastasis [33].

A randomized controlled trial (2017-2021) involving 101 patients with hepatocellular carcinoma demonstrated that the combination of vitamin K and transarterial chemoembolization exhibited significant anticancer effects when compared to transarterial chemoembolization alone [34]. The results demonstrated that vitamin K supplementation enhanced the anticancer effects of transarterial chemoembolization by reducing the levels of des-γ-carboxy prothrombin, a well-known factor involved in tumor growth and angiogenesis, which is produced in hepatocellular carcinoma under hypoxia induced by transarterial chemoembolization [34].

Lithium, primarily utilized in the medical treatment of psychiatric disorders, exhibits certain anticancer properties, functioning through mechanisms such as apoptosis, autophagy, cell cycle arrest, while also inhibiting proliferation, invasion and metastasis [35]. Lithium has shown anticancer activity *in vitro* against various types of cancer, including myeloma, neuroblastoma, glioblastoma, skin cancers, gastrointestinal cancers, breast cancer, hepatocellular carcinoma, lung cancer, nasopharyngeal cancer, pancreatic cancer, prostate cancer, colon cancer, and lymphatic tissue cancers. Clinical trials indicate that lithium may enhance anticancer effects when used alongside standard therapies in leukemia, small cell lung carcinoma, thyroid cancer, prostate cancer, and neuroendocrine tumors [36].

In vivo study conducted on a subcutaneous tumor xenograft model of colorectal carcinoma demonstrated that treatment with the probiotic strain *Lactobacillus plantarum* L168 significantly reduced tumor volume in tumor-bearing mice [37]. Results demonstrated that *Lactobacillus plantarum L168* and its metabolite, indole-3-lactic acid, contributed to preliminary activation of $CD8^+$ T cell immunity against tumor growth and improved the activity of tumor-infiltrating $CD8^+$ T cells by lowering their cholesterol levels [37].

In a preclinical mouse melanoma model, monotherapy with the probiotic strain *Bacteroides fragilis* BF839 led to significant tumor growth inhibition. When combined with anti-PD-1 antibody, it demonstrated a synergistic effect, promoting tumor regression. Furthermore, oral administration of BF839 notably enhanced the efficacy of immune checkpoint inhibitors in patients with advanced solid tumors, particularly in the long-term adjuvant treatment cohort, which showed significantly improved overall survival compared to those receiving short-term adjuvant therapy [38]. Using probiotic BF839 to modulate gut microbiota could present a novel approach to improving the effectiveness of immune checkpoint inhibitors, particularly in long-term adjuvant tumor treatment [38].

VACCINES

Evidence supporting oncologic applications has been documented for 15 licensed vaccines. Ten of these: BCG, influenza, diphtheria, pneumococcus, tetanus, human papillomavirus (HPV), measles, smallpox, varicella-zoster and typhoid vaccines already have completed or ongoing clinical evaluations in cancer settings [39]. Among the remaining vaccines, pertussis, yellow fever, and rotavirus show preclinical activity that justifies structured clinical testing, while mechanistic data for the cholera vaccine, together with observational findings in colorectal cancer, also supports further translational work. Several observations are of particular

relevance: intravesical typhoid vaccine outperformed BCG in a preclinical bladder cancer model; perioperative influenza vaccination may counteract surgery-induced NK-cell suppression; intratumoral measles vaccine has produced objective responses in cutaneous T-cell lymphoma; and HPV vaccination has elicited responses in cutaneous squamous cell carcinoma. Across these examples, vaccines act by initiating or enhancing anti-tumor immune activity, with outcomes influenced not only by their immunobiological properties but also by administration strategies and their integration with other (immuno)therapeutic modalities, which warrant closer examination in future studies [39]. In contrast, available evidence for hepatitis B and mumps (excluding the measles component) remains limited.

Many vaccines, including the COVID-19 vaccine, may selectively target tumor-associated antigens without affecting healthy cells. Identifying anticancer effects in vaccines already approved for other indications could significantly reduce both the time and cost of developing new oncology treatments. Protective efficacy of live-attenuated SARS-CoV-2 vaccine was tested in Syrian golden hamsters and in mice [40]. 14 days after challenge sera from immunized hamsters and mice had high antibodies and neutralizing capacity. Immunization protected hamsters and mice against the virus eliciting neutralizing antibodies and T-cell responses. Spatial (local) host gene expression near virus-infected sites of top 100 genes in cancer-related pathways (mean pathway activity score) such as MAPK, JAK-STAT, TGF-β and TNF-α correlated with immune response [40].

Recent experiments in tumor-bearing mice demonstrated that SARS-CoV-2 mRNA vaccines sensitized tumors to immune checkpoint blockade. Administration of these vaccines within 100 days of starting checkpoint inhibitors correlated with improved median and three-year overall survival across multiple large retrospective patient groups, including patients with immune non-responsive tumors. These findings indicated that clinically available mRNA vaccines targeting non-tumor antigens acted as potent immune modulators, enhancing tumor responsiveness to checkpoint inhibition [41].

Research in anticancer treatment includes vaccines, not only well-known, like BCG, but personalized (based on an individual's specific characteristics). Immunization with an anticancer vaccine would represent a dream come true. Tailored mRNA cancer vaccine therapy (modified for specific populations or groups) represents an innovative approach aimed at targeting existing tumors in patients. mRNA vaccine is engineered to elicit an mRNA-mediated immune response that specifically targets cancer cells. As of 2024, several mRNA cancer vaccines are undergoing clinical trials [42].

Personalized mRNA cancer vaccines constitute an advanced therapeutic modality that mobilizes the immune system to target malignant cells via tumor-specific antigens. As malignancies evolve, they accrue somatic mutations that generate neoantigens absent in normal tissues. Because these neoantigens are patient-specific, they offer both an opportunity for precision immunotherapy and a challenge in vaccine development. Clinically, personalized mRNA vaccines have shown promising outcomes: for example, in gastrointestinal cancers they elicited neoantigen-specific T cell responses and reduced tumor burden [43], and in late-stage pancreatic ductal adenocarcinoma and in non-small-cell lung cancer induced tumor size reduction in combination with pembrolizumab [44]. Despite this promise, several impediments remain: the manufacturing workflows are laborious and expensive; mRNA delivery, stability and expression *in vivo* require further optimization. To address these issues, investigators are refining antigen-screening methodologies and exploring novel delivery platforms. Looking ahead, mRNA tumour vaccines are poised to become integral components of multimodal cancer therapy, complementing surgery, cytotoxic chemotherapy, radiotherapy and immune checkpoint inhibitors. They offer the potential to expand therapeutic options, improve survival and enhance quality of life for cancer patients. With continued technological maturation and clinical validation, personalized mRNA cancer vaccines may become a powerful tool in oncology [45].

New research suggests that oncolytic herpes simplex virus can be repurposed as a cancer vaccine with removing a virulence gene. Oncolytic viruses cause direct lysis of tumor cells, resulting in the release of soluble antigens, danger signals, and type I interferons that stimulate antitumor immune responses. A synergistic effect was observed between a modified oncolytic herpes simplex virus and a phosphoinositide 3-kinase (PI3K) inhibitor, resulting in suppression of tumor growth, prolonged survival, and the induction of robust antitumor immunity in a mouse model of ovarian cancer [46].

CONCLUSION

The fight against cancer can be strengthened through diverse strategies, including drug repurposing, anticancer agents, and vaccines. In alignment with the principle of '*Primum non nocere,*' all the aforementioned therapeutic approaches and treatments possess the potential to improve current oncological practices. In conclusion, repurposing approved non-oncological drugs and vaccines offers a promising strategy for enhancing anticancer treatment outcomes, particularly as adjunct therapies to improve efficacy and as preventive measures to reduce the risk of relapse, thus warranting further clinical research to optimize their therapeutic potential.

We hope that this review will serve as a valuable reference for advancing the clinical application of repurposed drugs and vaccines anticancer effects, and contribute to the accelerated development of combination therapies involving repurposed pharmaceuticals for cancer treatment.

ACKNOWLEDGMENT

This study was supported by the Republic of Serbia, Autonomous Province of Vojvodina, Provincial Secretariat for High Education and Scientific Research, grant no. 003877305 2025 09418 003 000 000 001 04 004 (NPB).

Conflict of interest: None declared.

REFERENCES

1. Al Khzem AH, Gomaa MS, Alturki MS, Tawfeeq N, Sarafroz M, Alonaizi SM, et al. Drug repurposing for cancer treatment: a comprehensive review. Int J Mol Sci. 2024;25(22):12441. [DOI: 10.3390/ijms252212441] [PMID: 39596504]
2. Mohi-Ud-Din R, Chawla A, Sharma P, Mir PA, Potoo FH, Reiner Ž, et al. Repurposing approved non-oncology drugs for cancer therapy: a comprehensive review of mechanisms, efficacy, and clinical prospects. Eur J Med Res. 2023;28(1):345. [DOI: 10.1186/s40001-023-01275-4] [PMID: 37710280]
3. Xia Y, Sun M, Huang H, Jin WL. Drug repurposing for cancer therapy. Signal Transduct Target Ther. 2024;9:92. [DOI: 10.1038/s41392-024-01808-1] [PMID: 38637540]
4. Dhas Y, Biswas N, MRD, Jones LD, Ashili S. Repurposing metabolic regulators: antidiabetic drugs as anticancer agents. Mol Biomed. 2024;5(1):40. [DOI: 10.1186/s43556-024-00204-z] [PMID: 39333445]
5. Popović DJ, Lalošević D, Miljković D, Popović KJ, Čapo I, Popović JK. Effect of metformin on fibrosarcoma in hamsters. Eur Rev Med Pharmacol Sci. 2017;21(23):5499–505. [DOI: 10.26355/eurrev_201712_13941] [PMID: 29243803]
6. Popović DJ, Lalošević D, Miljković D, Popović KJ, Čapo I, Popović JK. Caffeine induces metformin anticancer effect on fibrosarcoma in hamsters. Eur Rev Med Pharmacol Sci. 2018;22:2461–7. [DOI: 10.26355/eurrev_201804_14840] [PMID: 29762853]
7. Popović KJ, Popović DJ, Miljković D, Popović JK, Lalošević D, Poša M, et al. Disulfiram and metformin combination anticancer effect reversible partly by antioxidant nitroglycerin and completely by NF-κB activator mebendazole in hamster fibrosarcoma. Biomed Pharmacother. 2021;143:112168. [DOI: 10.1016/j.biopha.2021.112168] [PMID: 34536762]
8. Popović KJ, Popović DJ, Lalošević D, Popović JK. Experimental evaluation of the effects of anticancer modulation therapy on MAPK/PI3K/AKT/mTOR/NF-κB signaling with non-toxic drugs. Srp Arh Celok Lek. 2024;152(3–4):138–46. [DOI: 10.2298/SARH230325011P]
9. Popović KJ, Popović DJ, Miljković D, Popović JK, Lalošević D, Čapo I. Co-treatment with nitroglycerin and metformin exhibits physicochemically and pathohistologically detectable anticancer effects on fibrosarcoma in hamsters. Biomed Pharmacother. 2020;130:110510. [DOI: 10.1016/j.biopha.2020.110510] [PMID: 32707437]
10. Popović DJ, Popović KJ, Lalošević D, Popović JK. Effects of metformin and its combinations with other repurposed drugs on fibrosarcoma in hamsters. Srp Arh Celok Lek. 2024;152(3–4):130–7. [DOI: 10.2298/SARH230325027P]
11. Popović JK, Popović DJ, Popović KJ, Miljković D, Lalošević D, Dolićanin Z, et al. Immunohistochemical evidences of anticancer actions of metformin with other repurposed drug combinations and correlation with hamster fibrosarcoma tumor size. J Serb Chem Soc. 2024;89(5):643–56. [DOI: 10.2298/JSC231203007P]
12. Popović DJ, Popović KJ, Miljković D, Popović JK, Lalošević D, Poša M, et al. Diclofenac and metformin synergistic dose dependent inhibition of hamster fibrosarcoma, rescued with mebendazole. Biomed Pharmacother. 2023;167:115528. [DOI: 10.1016/j.biopha.2023.115528] [PMID: 37738800]
13. Zhu L, Yang K, Ren Z, Yin D, Zhou Y. Metformin as anticancer agent and adjuvant in cancer combination therapy: current progress and future prospect. Transl Oncol. 2024;44:101945. [DOI: 10.1016/j.tranon.2024.101945] [PMID: 38555742]
14. Han K, Fyles A, Shek T, Croke J, Dhani N, D'Souza D, et al. A phase II randomized trial of chemoradiation with or without metformin in locally advanced cervical cancer. Clin Cancer Res. 2022;28:5263–71. [DOI: 10.1158/1078-0432.CCR-22-1665] [PMID: 36037303]
15. Kucinska M, Pospieszna J, Tang J, Lisiak N, Toton E, Rubis B, et al. The combination therapy using tyrosine kinase receptors inhibitors and repurposed drugs to target patient-derived glioblastoma stem cells. Biomed Pharmacother. 2024;176:116892. [DOI: 10.1016/j.biopha.2024.116892] [PMID: 38876048]. Erratum in: Biomed Pharmacother. 2025;188:118228. [DOI: 10.1016/j.biopha.2025.118228] [PMID: 40494675]
16. Lin Y, Liu Y, Gao Z, Jing D, Bi R, Cui X, et al. Beta-adrenergic receptor blocker propranolol triggers anti-tumor immunity and enhances irinotecan therapy in mice colorectal cancer. Eur J Pharmacol. 2023;949:175718. [DOI: 10.1016/j.ejphar.2023.175718] [PMID: 37054937]

17. Fjæstad KY, Rømer AMA, Goitea V, Johansen AZ, Thorseth ML, Carretta M, et al. Blockade of beta-adrenergic receptors reduces cancer growth and enhances the response to anti-CTLA4 therapy by modulating the tumor microenvironment. Oncogene. 2022;41(9):1364–75. [DOI: 10.1038/s41388-021-02170-0] [PMID: 35017664]

18. Shi CS, Kuan FC, Chin CC, Li JM. Modulation of mitochondrial apoptosis by β2-adrenergic receptor blockage in colorectal cancer after radiotherapy: an in vivo and in vitro study. Am J Cancer Res. 2023;13(8):3741–52. [PMID: 37693145]

19. Gone NV, Sharma T, Joshi R, Upreti A, Santra M, Sanjayan GJ. Repurposed ciprofloxacin derivatives as potent autophagic-type anticancer agents. Bioorg Med Chem Lett. 2025 Oct 10;130:130432. [DOI: 10.1016/j.bmcl.2025.130432] [PMID: 41077228]

20. Guan X, Han L. Itraconazole inhibits the Wnt/β-catenin signaling pathway to induce tumor-associated macrophages polarization to enhance the efficacy of immunotherapy in endometrial cancer. Front Oncol. 2025;15:1590095. [DOI: 10.3389/fonc.2025.1590095] [PMID: 40697374]

21. Chien MH, Hung WY, Lai TC, Tsai CH, Lee KL, Hsieh FK, et al. The off-target effect of loratadine triggers autophagy-mediated apoptosis in lung adenocarcinoma cells by deactivating JNK, p38, and STAT3 signaling through both PP2A-dependent and independent pathways. Int J Mol Med. 2025;55(4):54. [DOI: 10.3892/ijmm.2025.5495] [PMID: 39886963]

22. Liu X, Zhong R, Huang J, Chen Z, Xu H, Lin L, et al. Loratadine is associated with improved prognosis and exerts antineoplastic effects via apoptotic and pyroptotic crosstalk in lung cancer. J Exp Clin Cancer Res. 2024;43(1):5. [DOI: 10.1186/s13046-023-02914-8] [PMID: 38163866]

23. Chiang CH, Chiang CH, Peng CY, Hsia YP, See XY, Horng CS, et al. Efficacy of cationic amphiphilic antihistamines on outcomes of patients treated with immune checkpoint inhibitors. Eur J Cancer. 2022;174:1–9. [DOI: 10.1016/j.ejca.2022.07.006] [PMID: 35964360]

24. Li H, Xiao Y, Li Q, Yao J, Yuan X, Zhang Y, et al. The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. Cancer Cell. 2022;40(1):36–52.e9. [DOI: 10.1016/j.ccell.2021.11.002] [PMID: 34822775]

25. Trybus E, Król T, Trybus W. The multidirectional effect of azelastine hydrochloride on cervical cancer cells. Int J Mol Sci. 2022;23(11):5890. [DOI: 10.3390/ijms23115890] [PMID: 35682572]

26. Zhang Y, Sun H, Ji Y, Nie F, Wang R, Han W. Effects of aspirin on colon cancer using quantitative proteomic analysis. Cancer Pathog Ther. 2023;2(2):121–31. [DOI: 10.1016/j.cpt.2023.06.003] [PMID: 38601481]

27. Martling A, Hed Myrberg I, Nilbert M, Grönberg H, Granath F, Eklund M, et al; ALASCCA Study Group. Low-dose aspirin for PI3K-altered localized colorectal cancer. N Engl J Med. 2025;393(11):1051–64. [DOI: 10.1056/NEJMoa2504650] [PMID: 40961426]

28. Kaur D, Choudhury C, Yadav R, Kumari L, Bhatia A. Aspirin as a potential drug repurposing candidate targeting estrogen receptor alpha in breast cancer: a molecular dynamics and in vitro study. J Biomol Struct Dyn. 2025;43(11):5268–79. [DOI: 10.1080/07391102.2024.2308780] [PMID: 38279948]

29. Abdulnabi OW, Abd-Alsalam Alsalame HA, AL-Baiati M. Study effects of nano chitosan-paracetamol to inhibition spread of colon cancer. J Kufa Chem Sci. 2025;4(2):82–9. [DOI: 10.36329/jkcm/2025/v4.i2.15418]

30. Ma J, Zhang C, Shi G, Yue D, Shu Y, Hu S, et al. High-dose VitC plus oncolytic adenoviruses enhance immunogenic tumor cell death and reprogram tumor immune microenvironment. Mol Ther. 2022;30(2):644–61. [DOI: 10.1016/j.ymthe.2021.09.015] [PMID: 34547462]

31. Peng D, He A, He S, Ge G, Wang S, Ci W, et al. Ascorbic acid induced TET2 enzyme activation enhances cancer immunotherapy efficacy in renal cell carcinoma. Int J Biol Sci. 2022;18(3):995–1007. [DOI: 10.7150/ijbs.67329] [PMID: 35173532]

32. Helmy MW, Youssef MH, Yamari I, Amr A, Moussa FI, El Wakil AE, et al. Repurposing of sericin combined with dactolisib or vitamin D to combat non-small lung cancer cells through computational and biological investigations. Sci Rep. 2024;14:27034. [DOI: 10.1038/s41598-024-76947-0]

33. Chauhan A, Anjaly K, Saini A, Kumar R, Kuanr BK, Sharma D. Vitamin K3-loaded magnetic nanoparticle-mediated synergistic magnetothermodynamic therapy evokes massive ROS and immune modulation for augmented antitumor potential. ACS Appl Mater Interfaces. 2023;15(23):27515–32. [DOI: 10.1021/acsami.3c01702] [PMID: 37264797]

34. Haruna Y, Yakushijin T, Yamakawa M, Nakazawa T. Anticancer effects of vitamin K combined with transarterial chemoembolization in hepatocellular carcinoma: a randomized controlled trial. Br J Cancer. 2025;132:1141–7. [DOI: 10.1038/s41416-025-03022-4] [PMID: 40263401]

35. Ramushu P, Mangoakoane DD, Makola RT, Matsebatlela TM. Lithium induces oxidative stress, apoptotic cell death, and G2/M phase cell cycle arrest in A549 lung cancer cells. Molecules. 2025;30(8):1797. [DOI: 10.3390/molecules30081797] [PMID: 40333785]

36. Villegas-Vázquez EY, Quintas-Granados LI, Cortés H, González-Del CM, Leyva-Gómez G, Rodríguez-Morales M, et al. Lithium: a promising anticancer agent. Life (Basel). 2023;13(2):537. [DOI: 10.3390/life13020537] [PMID: 36836894]

37. Zhang Q, Zhao Q, Li T, Lu L, Wang F, Zhang H, et al. Lactobacillus plantarum-derived indole-3-lactic acid ameliorates colorectal tumorigenesis via epigenetic regulation of CD8+ T cell immunity. Cell Metab. 2023;35(6):943–60.e9. [DOI: 10.1016/j.cmet.2023.04.015] [PMID: 37192617]

38. Peng K, Li Y, Yang Q, Yu P, Zeng T, Lin C, et al. The therapeutic promise of probiotic Bacteroides fragilis (BF839) in cancer immunotherapy. Front Microbiol. 2025;16:1523754. [DOI: 10.3389/fmicb.2025.1523754] [PMID: 40231233]

39. Vandeborne L, Pantziarka P, Van Nuffel AMT, Bouche G. Repurposing infectious diseases vaccines against cancer. Front Oncol. 2021;11:688755. [DOI: 10.3389/fonc.2021.688755] [PMID: 34055652]

40. Schön J, Barut GT, Trüeb BS, Halwe NJ, Berenguer Veiga I, Kratzel A, et al. A safe, effective and adaptable live-attenuated SARS-CoV-2 vaccine to reduce disease and transmission using one-to-stop genome modifications. Nat Microbiol. 2024;9:2099–112. [DOI: 10.1038/s41564-024-01755-1] [PMID: 38997518]

41. Grippin AJ, Marconi C, Copling S, Li N, Braun C, Woody C, et al. SARS-CoV-2 mRNA vaccines sensitize tumours to immune checkpoint blockade. Nature. 2025;647(8089):488–97. [DOI: 10.1038/s41586-025-09655-y] [PMID: 41125896]

42. Yao R, Xie C, Xia X. Recent progress in mRNA cancer vaccines. Hum Vaccin Immunother. 2024;20(1):2307187. [DOI: 10.1080/21645515.2024.2307187] [PMID: 38282471]

43. Cafri G, Gartner JJ, Zaks T, Hopson K, Levin N, Paria BC, et al. mRNA vaccine-induced neoantigen-specific T cell immunity in patients with gastrointestinal cancer. J Clin Invest. 2020;130(11):5976–88. [DOI: 10.1172/JCI134915] [PMID: 33016924]

44. Wang X, Wang W, Zou S, Xu Z, Cao D, Zhang S, et al. Combination therapy of KRAS G12V mRNA vaccine and pembrolizumab: clinical benefit in patients with advanced solid tumors. Cell Res. 2024;34:661–4. [DOI: 10.1038/s41422-024-00990-9] [PMID: 38914844]

45. Li J, Liu Y, Dai J, Yang L, Xiong F, Xia J, et al. mRNA vaccines: current applications and future directions. MedComm (2020). 2025 Oct 30;6(11):e70434. [DOI: 10.1002/mco2.70434] [PMID: 41179708]

46. Huang S, Hu H, Tang G, Liu K, Luo Z, Zeng W. An oncolytic herpes simplex virus type 1 strain expressing a single-chain variable region antibody fragment against PD-1 and a PI3K inhibitor synergize to elicit antitumor immunity in ovarian cancer. Arch Virol. 2023;168:128. [DOI: 10.1007/s00705-023-05754-1] [PMID: 37002434]

Abbreviations

ABC - ATP-Binding Cassette
Akt - Protein Kinase B (PKB)
ATG (5, 9A, 12, 13) - Autophagy-Related Genes
Bax - B-Cell Lymphoma 2-Associated X Protein
Bcl-2 - B-Cell Lymphoma 2
Beclin1 - Autophagy Related 1
cABL - cytoplasmic Abelson tyrosine kinase
Caspase 3, 8, 9, 12 - Cysteine-Asparatic Proteases
CD31 (PECAM1) - Platelet Endothelial Cell Adhesion Molecule 1
CD34 - Cluster of Differentiation 34, a protein marking hematopoietic stem cells
CDKs - Cyclin-Dependent Kinases
COX-2 (PTGS2) - Cyclooxygenase-2
CXC - CXC chemokines, a family of small signaling proteins, CXC motif refers to the sequence of cysteine residues in the protein, Cys-X-Cys arrangement, where X is amino acid
CXCL12 (SDF1) - C-X-C Motif Chemokine Ligand 12, (known as Stromal-Derived Factor 1, SDF1)
CXCR4 - C-X-C Motif Chemokine Receptor 4
Cyclin D1 - a crucial cell cycle protein, drives cell cycle progression by activating CDKs
Cytochrome C –electron-transporting protein crucial for cellular respiration and apoptosis
EGFR - Epidermal Growth Factor Receptor
Eps8 - Epidermal Growth Factor Receptor Pathway Substrate 8
ERK - Extracellular Signal-Regulated Kinase
FAK (PTK2) - Focal Adhesion Kinase
FAS - Fatty Acid Synthase
GLUTs (1-13) - Glucose Transporters
Hedgehog - Hedgehog Signaling Pathway
HES1 - Hairy and Enhancer of Split 1 (transcription factor)
HIFs (HIF-1α, HIF-1β, HIF-2α, HIF-2β) - Hypoxia-Inducible Factors (1α, 1β, 2α, 2β)
Hippo - Hippo Signaling Pathway (in cell growth)
IGF-1 - Insulin-Like Growth Factor 1
IL1β - Interleukin 1 Beta
ILs (IL1, IL6, IL8, IL10, IL17) - Interleukins
iNOS - Inducible Nitric Oxide Synthase
IκB (IKK) - Inhibitor of κB, regulates NF-κB
IKKα, IKKβ, IKKγ (= NEMO) - IκB Kinase Subunits (α, β, γ)
IκBα - Inhibitor of κB Alpha, protein that regulates the Nuclear Factor kappa B (NF-κB) pathway
JAK - Janus Kinase
JNK - c-Jun N-terminal Kinase
K13 - Kinesin Family Member 13
KLF4 - Krüppel-Like Factor 4
Ki-67 - Antigen for Monoclonal Antibody Ki-67
LC3 - Microtubule-Associated Protein 1 Light Chain 3
LEFs - Lymphoid Enhancer-Binding Factors
MAPK - Mitogen-Activated Protein Kinase
Mcl-1 - Myeloid Cell Leukemia-1
MDPRs - Multi-Drug Resistance Proteins
MDR - Multi-Drug Resistance
MEK - Mitogen-Activated Protein Kinase
mTOR - Mechanistic Target of Rapamycin
MUC2 - Mucin 2
MYC (C-, N-, L-) - Myelocytomatosis Oncogene (C-, N-, L- Types)
Nanog - Homeobox Transcription Factor Nanog
NF-κB - Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
Notch - Notch Receptor Signaling Pathway (in development and tissue homeostasis)
Nrf2 - Nuclear Factor Erythroid 2-Related Factor 2
Oct4 - Octamer-Binding Transcription Factor 4
p21 - Cyclin-Dependent Kinase Inhibitor 1A
p27 - Cyclin-Dependent Kinase Inhibitor 1B
P2X4, P2X7- P2X Purinoceptor (4, 7)
p38 - Mitogen-Activated Protein Kinase p38
p53 - Tumor Protein P53
p62 - Sequestosome 1 Protein
p63 - Tumor Protein p63, a transcription factor, a member of the p53 family of tumor-suppressor proteins
p65 (Rel A) - p65 Subunit of NF-κB (RelA)
p73 - Tumor Protein p73
PAK1 - p21-Activated Kinase 1
PANX1 - Pannexin 1
PARPs - Poly(ADP-Ribose) Polymerases
PCNA - Proliferating Cell Nuclear Antigen
PGE2 - Prostaglandin E2
P-gp - P-Glycoprotein (permeability glycoprotein, also known as ABCB1), a drug efflux pump
PI3K - Phosphoinositide 3-Kinase
PKC - Protein Kinase C
PTEN - Phosphatase and Tensin Homolog
PTK - Protein Tyrosine Kinase
Raf - Rapidly Accelerated Fibrosarcoma Kinase
RAS - Rat Sarcoma Viral Oncogene Homolog
ROS - Reactive Oxygen Species
SMAD - SMAD Family of Proteins (involved in TGF-β signaling)
Sox2 - SRY (Sex-Determining Region Y)-Box Transcription Factor 2
STATs - Signal Transducers and Activators of Transcription
TCFs - T-Cell Factors (transcription factors in Wnt signaling)
TGF-α, TGF-β - Transforming Growth Factor (α, β)
TLRs - Toll-Like Receptors
TNF - Tumor Necrosis Factor
TNF-α - Tumor Necrosis Factor Alpha
TRAIL - TNF-Related Apoptosis-Inducing Ligand
VDR - Vitamin D Receptor
VEGF - Vascular Endothelial Growth Factor
VEGFR - Vascular Endothelial Growth Factor Receptor
Wnt - Wingless-Int Family
YAP - Yes-Associated Protein (in Hippo signaling)
β-catenin - Beta-Catenin (Cadherin-Associated Protein), in Wnt signaling pathway and cell adhesion

Table 1. Selected newer examples of drug repurposing for cancer therapy

Pharm. class / Drug Name	Type of cancer cells tested (in order of incidence) as promising new therapeutic indication															
	Breast	Lung	Colon	Prostate	Melanoma	Leukemia	Liver	Pancreatic	Ovarian	Kidney	Endocrine	Brain	Glioblastoma	Neuroblastoma	Cervical	Various / other cancer
Anti-diabetics																
Metformin	+	+	+	+				+							+	
Gliclazide	+	+	+	+				+							+	
Anti-helmintics																
Ivermectin	+		+	+				+								
Flubendazole	+	+	+		+	+	+							+		
Anti-malarial																
Chloroquine	+						+	+					+			
Anti-fungal																
Itraconazole		+		+												+
Clotrimazole	+	+	+													
Antibiotics																
Doxycycline			+	+												+
Minocycline	+								+				+			
Ciprofloxacin			+	+		+				+						+
Antiviral																
Ritonavir	+					+		+	+							
Nelfinavir	+	+							+							
Acyclovir	+												+			
Ribavirin	+	+				+			+							
Cidofovir													+			+
Beta-blockers																
Propranolol	+	+	+	+	+	+		+	+					+		+
Carvedilol	+	+		+	+	+							+			
Antihyperlipidemics																
Simvastatin	+	+		+												+
Fenofibrate	+	+														
Angiotensin receptor blockers																
Losartan	+	+			+			+	+							+
Candesartan			+	+			+			+						

Pharm. class / Drug Name	Type of cancer cells tested (in order of incidence) as promising new therapeutic indication															
	Breast	**Lung**	**Colon**	**Prostate**	**Melanoma**	**Leukemia**	**Liver**	**Pancreatic**	**Ovarian**	**Kidney**	**Endocrine**	**Brain**	**Glioblastoma**	**Neuroblastoma**	**Cervical**	**Various / other cancer**
ACE inhibitors																
Captopril			+	+			+			+						
Enalapril			+													
Direct vasodilators																
Minoxidil	+								+							
Hydralazine	+			+					+							+
Potassium K^+ channel inhibitors																
Glipalamide	+	+			+											+
Verapamil	+	+		+		+		+						+		
Calcium channel blockers																
Mibefradil	+					+							+			+
Nifedipine	+		+													
Immunosuppressive																
Rapamycin	+															+
Nonsteroidal antiinflammatory drugs (NSAID)																
Acetylsalicylic acid	+		+	+			+	+	+							+
Diclofenac	+		+	+			+	+	+				+			+
Celecoxib	+	+	+	+					+							+
Etoricoxib	+	+	+					+								
Antipsychotic																
Haloperidol								+					+			
Anti-epileptic																
Lamotrigine	+											+				
Mood stabilizer																
Lithium		+		+		+					+			+		+

