Curcumin as a Protective Agent Against Doxorubicin-Induced Cardiotoxicity: Current Insights and Future Perspectives

Vishal S. Adak[1], Shrikant R. Borate[2], Dr. Rajkumar V. Shete[3], Tejas S. Shinde[4]
[1,2,3,4]*Professor, Rajgad Dnyanpeeth's College of Pharmacy, Bhor. Pune, Maharashtra, India*

***Abstract*—Doxorubicin is a powerful and frequently used chemotherapeutic medication that works against a wide spectrum of cancers, including breast cancer, leukemia, lymphoma, and sarcoma. Despite its impressive anticancer activity, doxorubicin's therapeutic use is severely limited due to cumulative dose-dependent cardiotoxicity, which can lead to cardiomyopathy, arrhythmias, and permanent congestive heart failure.[1] Doxorubicin-induced cardiotoxicity is primarily caused by the excessive formation of reactive oxygen species, mitochondrial dysfunction, lipid peroxidation, inflammatory responses, calcium imbalance, and activation of apoptotic pathways in cardiomyocytes. These side effects urge the development of safer supplementary medicines that can preserve heart function while maintaining anticancer potency.**

Curcumin, Curcuma longa's main functional element, has received a lot of scientific attention because to its powerful antioxidant, anti-inflammatory, antiapoptotic, and cardioprotective characteristics.[2] Curcumin reduces free radicals, boosts antioxidant defenses like superoxide dismutase, catalase, and glutathione peroxidase, inhibits pro-inflammatory mediators like TNF-α and NF-KB, and safeguards mitochondrial health. Curcumin has demonstrated promising effects in reducing myocardial injury linked with doxorubicin therapy by modulating various signaling pathways.[3]

This review reviews the current data for curcumin's protective impact against doxorubicin-induced cardiotoxicity, focusing on its pharmacological mechanisms, preclinical findings, formulation techniques, and therapeutic prospects. Several in vivo and in vitro investigations have shown that curcumin lowers serum cardiac biomarkers, improves histopathological changes, restores antioxidant status, and improves overall heart function. [4] However, clinical translation of curcumin remains difficult due to its limited aqueous solubility, poor bioavailability and quick metabolism.[5]

Advanced delivery technologies, such as nanoparticles, liposomes, micelle-sized particles, and phytosomes, for example, can bypass such constraints. To summarize, curcumin is a promising natural adjuvant for reducing doxorubicin-associated heart damage and deserves additional clinical evaluation for safe incorporation into cancer therapy.[6]

I. INTRODUCTION

Doxorubicin is a very effective and widely prescribed anthracycline-class anticancer medication. It is commonly used to treat numerous cancers, including breast cancer, ovarian cancer, leukemia, lymphoma, and soft tissue sarcomas. [7] Doxorubicin's anticancer effect is principally mediated via DNA intercalation, topoisomerase II inhibition, and free radical production, which results in the suppression of rapidly dividing cancer cells. Despite its remarkable therapeutic efficacy, doxorubicin's long-term clinical use is severely limited due to cumulative dose-dependent cardiotoxicity.[8]

Doxorubicin-induced cardiac toxicities is still a major problem in oncology therapy, since it can cause substantial cardiovascular consequences such as electrocardiographic abnormalities, arrhythmias, left ventricular dysfunction, dilated cardiomyopathy, and congestive heart failure.[9] The heart is especially sensitive to oxidative harm due to its large mitochondrial load and limited antioxidant defense capacity. Several pathways have been hypothesized for doxorubicin-induced cardiac injury, including increased reactive oxygen species generation, mitochondrial dysfunction, lipid peroxidation, calcium overload, inflammatory signaling, and cardiomyocyte death.[10]

To prevent these negative consequences, significant research has been focused on the use of natural bioactive substances having cardioprotective properties. Curcumin, the main curcuminoid derived from Curcuma longa, has emerged as a promising treatment option. Curcumin has been used in herbal therapy for centuries and is widely recognized for its antioxidant, anti-inflammatory, antibacterial, anticancer, and cardioprotective qualities. It has the ability to neutralize free radicals, activate endogenous antioxidant enzymes, regulate inflammatory mediators, and block apoptotic pathways involved in cardiac damage.[11]

Curcumin has been shown in recent research to considerably reduce doxorubicin-induced heart damage while retaining myocardial shape and function. However, issues such as low water solubility, limited absorption, and quick metabolism have hampered its practical use. Novel formulation technologies such as nanoparticles, liposomes, micelles, and phytosomes are being investigated to improve bioavailability and therapeutic efficacy.

As a result, the purpose of this study is to offer a complete overview of the mechanisms underlying doxorubicin-induced cardiotoxicity and curcumin's protective effect, with a focus on pharmacological actions, preclinical evidence, formulation methodologies, and future clinical prospects.[12]

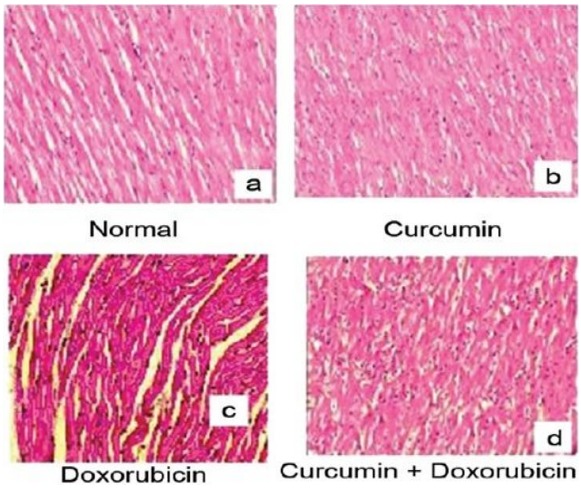

FIG.NO.1

(a) Photomicrograph of normal group heart showing normal myocardial fibers and architecture.

(b) Doxorubicin-treated group showing loss of myocardial fibers and vacuolated cells. (c) Curcumin-treated group showing no vacuolated cells and myofibers loss and normal architecture.

(d) Curcumin + doxorubicin treated group showing scanty myocardial fibers loss and vacuolated cells.[13]

II. MECHANISMS FOR DOXORUBICIN-INDUCED CARDIOTOXICITY

Doxorubicin-induced cardiotoxicity is a complex process comprising numerous interconnected molecular and cellular pathways that eventually result in myocardial injury and reduced heart function.[14] Toxicity often worsens with cumulative dose, length of therapy, and patient-related risk factors like age, pre-existing cardiovascular disease, and concurrent chemotherapy. The main mechanisms are explained below. [14,15]

1. Oxidative stress and the generation of reactive oxygen species.

One of the most frequently acknowledged mechanisms is the overproduction of reactive oxygen species (ROS), including superoxide radicals, hydrogen peroxide, and hydroxyl radicals. Doxorubicin redox cycles in the mitochondria, generating free radicals that harm lipids, proteins, and nucleic acids. Because cardiac tissue contains relatively low quantities of antioxidant enzymes, the myocardium is especially vulnerable to oxidative damage.

2. Lipid Peroxidation Doxorubicin generates

ROS that attacks polyunsaturated fatty acids in cellular and mitochondrial membranes, causing lipid peroxidation. This process destroys membrane integrity, changes permeability, hinders ion transport, and causes cardiomyocytes to lose their normal.

3. Mitochondrial dysfunction.

The heart relies largely on mitochondria for sustained ATP synthesis. Doxorubicin accumulates in mitochondria and disrupts the electron transport chain, limiting energy production. It also damages mitochondrial DNA, depolarizes the membrane, and releases pro-apoptotic proteins, all of which contribute to decreased cardiac contraction.

4. Iron-mediated toxicity

Doxorubicin can form compounds with iron, catalyzing the creation of extremely reactive hydroxyl radicals via Fenton-type processes. This exacerbates oxidative stress and cellular damage in heart tissue.

5. Apoptosis of cardiomyocytes.

Doxorubicin promotes intrinsic and extrinsic apoptotic pathways by damaging mitochondria, activating caspases, and altering the expression of Bcl-2 family proteins. Apoptosis causes cardiomyocyte loss, which contributes to increasing cardiac failure.

6. Inflammatory responses.

Doxorubicin treatment activates inflammatory signaling pathways, including TNF-α, IL-1β, IL-6, and NF-κB. Chronic inflammation exacerbates myocardial remodeling, fibrosis, and ventricular failure.

7. Calcium Homeostasis Disturbance

Doxorubicin impairs calcium transport in cardiomyocytes by influencing sarcoplasmic reticulum channels and membrane pumps. Abnormal intracellular calcium levels disrupt contraction-relaxation cycles and can cause arrhythmias.

8. Topoisomerase IIβ Involvement

Doxorubicin's suppression of cardiac topoisomerase IIβ results in DNA damage and altered gene expression relevant to mitochondrial biogenesis and cell survival, leading to card biotoxicity.

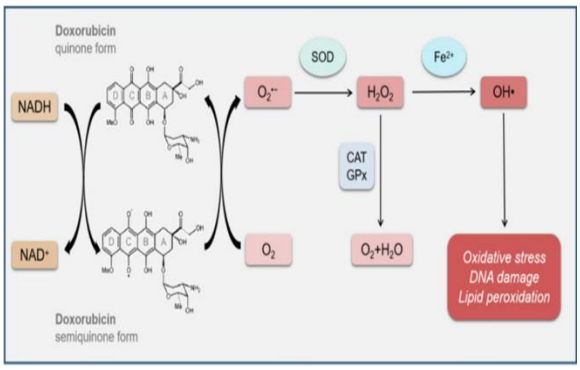

FIG.NO.2

DOX-induced redox cycling. Single-electron reduction can be used by mitochondrial NADH-dependent enzymes to transform the quinone moiety in DOX ring C into semiquinone form. [14,15]

Curcumin's source and pharmacological profile

Curcumin is the main curcuminoid produced from Curcuma longa. It has sparked substantial scientific attention due to its extensive pharmacological activity, which include antioxidant, anti-inflammatory, antibacterial, anticancer, hepatoprotective, neuroprotective, and cardioprotective properties. Curcumin comprises phenolic and diketone functional groups, which contribute to free radical scavenging and metal chelation capabilities. Its multitarget action makes it an excellent candidate for protecting against drug-induced organ toxicity.[16]

Curcumin plays an antioxidant role in cardiac protection.

Oxidative stress is the principal cause of doxorubicin-induced heart damage. Curcumin inhibits reactive oxygen species and increases natural antioxidant defense enzymes such superoxide dismutase, catalase, and glutathione peroxidase. It also lowers malondialdehyde levels, a sign of lipid peroxidation. Curcumin prevents oxidative damage to cardiac membranes and intracellular organelles by restoring redox equilibrium.[17]

Anti-inflammatory mechanisms

Inflammatory cytokines contribute to the advancement of heart injuries. Curcumin reduces pro-inflammatory mediators (TNF-α, IL-1β, IL-6) and inhibits NF-KB signaling. Reducing inflammation may help to avoid fibrosis, ventricular remodeling, and impairment of heart function after chemotherapy.[18]

Anti-apoptotic and mitochondrial protective properties

Doxorubicin triggers apoptosis pathways, resulting in cardiomyocyte death. Curcumin regulates the Bax/Bcl-2 ratio, suppresses caspase activation, and maintains mitochondrial membrane potential. It also promotes ATP production and mitochondrial integrity, which are required for continued heart contraction.[19]

Evidence from preclinical studies

Several in vivo and in vitro investigations have shown that curcumin protects against doxorubicin-induced cardiotoxicity. Curcumin treatment has been linked to lower blood biomarkers such CK-MB, LDH, and troponins, improved histological architecture,

normalization of ECG abnormalities, and increased cardiac antioxidant status. These data suggest a strong cardioprotective potential. [20]

Formulation Strategies to Improve Curcumin Delivery
Curcumin is pharmacologically promising; however, it has poor water solubility, low gastrointestinal absorption, quick metabolism, and restricted bioavailability. To circumvent these hurdles, improved drug delivery systems such as nanoparticles, liposomes, micelles, phytotomies, Nano emulsions, and solid dispersions are being studied. These systems could improve stability, absorption, tissue targeting, and therapeutic efficacy. [21]

III. DISCUSSION

Despite significant advances in experimental research, Curcumin's therapeutic application as a cardioprotective adjuvant in cancer treatment remains limited. A major portion of the present information is based on in vitro cell line research and in vivo animal models, which, while useful for mechanistic knowledge, cannot fully recreate the complexity of human physiology and cancer therapy responses. Variations in species, study duration, dosing regimens, route of administration, and techniques of toxicity evaluation result in high variation between studies, making direct comparison of results problematic. As a result, the dearth of established protocols has hindered the development of unambiguous therapeutic guidelines. [21,22]

Curcumin's physicochemical and pharmacokinetic limitations present yet another significant issue. Curcumin has low water solubility, limited intestinal absorption, rapid metabolism, and fast systemic elimination, resulting in low oral bioavailability. Because of these limitations, several studies have required relatively high curcumin dosages to generate detectable cardioprotective benefits. Such doses may not always be practicable or cost-effective in clinical settings, and they may diminish patient adherence to long-term medication. To address these concerns, innovative delivery technologies such as nanoparticles, liposomes, micelles, phospholipid complexes, and sustained-release formulations are being actively researched to increase systemic exposure and tissue targeting.

Standardization is another key element to consider before normal medical applications. Curcumin preparations vary in source material, extraction processes, purity, curcuminoid content, and excipient profile.

Curcumin and Doxorubicin may interact, which is another source of worry. Ideally, any cardioprotective adjunct should reduce toxicity while maintaining anticancer activity. According to certain experimental investigations, curcumin may increase doxorubicin's anticancer activity by sensitizing tumor cells, inhibiting survival pathways, and reducing multidrug resistance. However, other potential pharmacokinetic or pharmacodynamic interactions have not been thoroughly investigated. Curcumin must be carefully evaluated to ensure that it does not impair chemotherapeutic efficacy or cause unpredictable drug disposition. [22]

IV. FUTURE PROSPECTS

Future research on curcumin's anticancer activities should focus on leveraging modern scientific developments to overcome existing boundaries and unlock its full therapeutic potential, specifically achieving the following: [23]

1. study its ability to modulate the tumor microenvironment, including immunity;
2. identify biomarkers to predict curcumin-based therapies;
3. develop next-generation nanocarriers (lipid-based nanoparticles, polymeric micelles, or exosomes).
4. investigate co-delivery systems with other anticancer agents for a synergistic effect;
5. develop personalized curcumin formulations;
6. investigate its role in modulating epigenetic mechanisms;
7. use artificial intelligence (AI) and machine learning to predict curcumin's interactions with molecular targets and optimize its structure for enhanced anticancer activity; and
8. investigate synergy between curcumin and other plant-derived compounds for higher anticancer effect

V. CONCLUSION

Doxorubicin is still one of the most effective chemotherapeutic medicines for treating a variety of malignancies; nevertheless, its clinical utility is severely limited by cumulative dose-dependent cardiotoxicity.[24] This toxicity is caused by oxidative stress, mitochondrial malfunction, inflammation, apoptosis, calcium imbalance, and gradual cardiac damage, which can eventually lead to cardiomyopathy and heart failure. [25]As a result, the hunt for safe and effective cardioprotective medicines has become a critical component of supportive oncology research.[26]

Curcumin has emerged as a promising natural therapeutic candidate because of its strong antioxidant, anti-inflammatory, antiapoptotic, and mitochondrial protective properties. Experimental studies have consistently demonstrated that curcumin can attenuate biochemical, structural, and functional cardiac alterations induced by doxorubicin. It has shown the ability to reduce oxidative injury, suppress inflammatory mediators, preserve endogenous antioxidant defenses, and improve overall myocardial integrity.[27]

Despite these encouraging findings, the routine clinical application of curcumin remains constrained by poor bioavailability, variability in formulations, and limited human clinical evidence. Novel delivery methods, including as nanoparticles, liposomes, micelles, and phytozoa systems, may assist overcome these hurdles and improve therapeutic effectiveness.[28] Furthermore, curcumin may assist preserve mitochondrial energy generation and prevent cellular death pathways linked to chemotherapy-induced heart impairment. Its multitarget pharmacological activity makes it particularly appealing as a support agent in complex illness states.[29]

Some studies have also suggested that curcumin may improve overall patient health by lowering inflammatory load and oxidative stress.

These benefits justify sustained research interest in curcumin-based cardio protection.

Furthermore, its natural origin and acceptable safety profile make it potentially suitable for long-term adjunctive use.[30]

REFERENCE

[1] Kciuk, M., Gielecińska, A., Mujwar, S., Kołat, D., Kałuzińska-Kołat, Ż., Celik, I., & Kontek, R. (2023). Doxorubicin-An Agent with Multiple Mechanisms of Anticancer Activity. Cells, 12(4), 659. https://doi.org/10.3390/cells12040659

[2] Bukowski K., Kciuk M., Kontek R. Mechanisms of Multidrug Resistance in Cancer Chemotherapy. Int. J. Mol. Sci. 2020; 21:3233. doi: 10.3390/ijms21093233. [DOI] [PMC free article] [PubMed] [Google Scholar]

[3] Sohail, M., Sun, Z., Li, Y., Gu, X., & Xu, H. (2021). Research progress in strategies to improve the efficacy and safety of doxorubicin for cancer chemotherapy. Expert review of anticancer therapy, 21(12), 1385–1398. https://doi.org/10.1080/14737140.2021.1991316

[4] Sinha, S. J., Kumar, B., Prasad, C. P., Chauhan, S. S., & Kumar, M. (2025). Emerging Research and Future Directions on Doxorubicin: A Snapshot. Asian Pacific journal of cancer prevention: APJCP, 26(1), 5–15. https://doi.org/10.31557/APJCP.2025.26.1.5

[5] Vauzour D. Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. Oxid Med Cell Longev. 2012; 2012:914273. PubMed, PubMedCentral, CrossRef

[6] Yang C, Zhu Q, Chen Y, Ji K, Li S, Wu Q, Pan Q, Li J. Review of the protective mechanism of curcumin on cardiovascular disease. Drug Des Devel Ther. 2024; 18:165-192. PubMed, PubMedCentral, CrossRef

[7] Douedi S, Carson MP. Anthracycline Medications (Doxorubicin) [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551633/

[8] Çeribas, A.O.; Sakin, F.; Türk, G.; Sönmez, M.; Atessahin, A. Impact of ellagic acid on adriamycin-induced testicular histopathological lesions, apoptosis, lipid peroxidation and sperm damages. Exp. Toxicol. Pathol. 2012, 64, 717–724. [CrossRef] [PubMed]

[9] Abdelaziz, M.H.; Salah EL-Din, E.Y.; El-Dakdoky, M.H.; Ahmed, T.A. The impact of

mesenchymal stem cells on doxorubicininduced testicular toxicity and progeny outcome of male prepubertal rats. Birth Defects Res. 2019, 111, 906–919. [CrossRef]

[10]. Salem, E.A.; Salem, N.A.; Hellstrom, W.J. Therapeutic effect of ozone and rutin on adriamycin-induced testicular toxicity in an experimental rat model. Andrologia 2017, 49, e12603. [CrossRef]

[11] Jukkala, A.M.; Meneses, K.M. Preserving fertility in young women diagnosed with breast Cancer. Oncology 2009, 23, 36–38.

[12] Hu Z. (2024). Exploring the mechanism of curcumin in the treatment of doxorubicin-induced cardiotoxicity based on network pharmacology and molecular docking technology. Medicine, 103(7), e36593. https://doi.org/10.1097/MD.0000000000036593

[13] Swamy, A. V., Gulliaya, S., Thippeswamy, A., Koti, B. C., & Manjula, D. V. (2012). Cardioprotective effect of curcumin against doxorubicin-induced myocardial toxicity in albino rats. Indian journal of pharmacology, 44(1), 73–77. https://doi.org/10.4103/0253-7613.91871

[14] Wang A, J., Zhang, J., Xiao, M., Wang, S., Wang B, J., Guo, Y., Tang, Y., & Gu, J. (2021). Molecular mechanisms of doxorubicin-induced cardiotoxicity: novel roles of sirtuin 1-mediated signaling pathways. Cellular and molecular life sciences: CMLS, 78(7), 3105–3125. https://doi.org/10.1007/s00018-020-03729-y

[15] Zhang, T.; Yan, D.; Yang, Y.; Ma, A.; Li, L.; Wang, Z.; Pan, Q.; Sun, Z. The comparison of animal models for premature ovarian failure established by several different source of inducers. Regul. Toxicol. Pharmacol. 2016, 81, 223–232. [CrossRef]

[16] El-Saadony, M. T., Yang, T., Korma, S. A., Sitohy, M., Abd El-Mageed, T. A., Selim, S., Al Jaouni, S. K., Salem, H. M., Mahmmod, Y., Soliman, S. M., Mo'men, S. A. A., Mosa, W. F. A., El-Wafai, N. A., Abou-Aly, H. E., Sitohy, B., Abd El-Hack, M. E., El-Tarabily, K. A., & Saad, A. M. (2023). Impacts of turmeric and its principal bioactive curcumin on human health: Pharmaceutical, medicinal, and food applications: A comprehensive review. Frontiers in nutrition, 9, 1040259. https://doi.org/10.3389/fnut.2022.1040259

[17] Cox, F. F., Misiou, A., Vierkant, A., Ale-Agha, N., Grandoch, M., Haendeler, J., & Altschmied, J. (2022). Protective Effects of Curcumin in Cardiovascular Diseases-Impact on Oxidative Stress and Mitochondria. Cells, 11(3), 342. https://doi.org/10.3390/cells11030342

[18] Peng, Y., Ao, M., Dong, B., Jiang, Y., Yu, L., Chen, Z., Hu, C., & Xu, R. (2021). Anti-Inflammatory Effects of Curcumin in the Inflammatory Diseases: Status, Limitations and Countermeasures. Drug design, development and therapy, 15, 4503–4525. https://doi.org/10.2147/DDDT.S327378

[19] Raja, K., Patnaik, R., Suresh, D., Varghese, R., Eid, A., Nau, T., Banerjee, Y., & Naidoo, N. (2026). The Protective Role of Curcumin in Osteoarthritis: Establishing Mitochondrial Homeostasis Through Autophagy Induction and Apoptosis Inhibition. International journal of molecular sciences, 27(2), 609. https://doi.org/10.3390/ijms27020609

[20] Swamy, A. V., Gulliaya, S., Thippeswamy, A., Koti, B. C., & Manjula, D. V. (2012). Cardioprotective effect of curcumin against doxorubicin-induced myocardial toxicity in albino rats. Indian journal of pharmacology, 44(1), 73–77. https://doi.org/10.4103/0253-7613.91871

[21] Tabanelli, R., Brogi, S., & Calderone, V. (2021). Improving Curcumin Bioavailability: Current Strategies and Future Perspectives. Pharmaceutics, 13(10), 1715. https://doi.org/10.3390/pharmaceutics13101715

[22] Tomeh, M. A., Hadianamrei, R., & Zhao, X. (2019). A Review of Curcumin and Its Derivatives as Anticancer Agents. International journal of molecular sciences, 20(5), 1033. https://doi.org/10.3390/ijms20051033

[23] Akter, K., Gul, K., & Mumtaz, S. (2025). Revisiting Curcumin in Cancer Therapy: Recent Insights into Molecular Mechanisms, Nanoformulations, and Synergistic Combinations. Current issues in molecular biology, 47(9), 716. https://doi.org/10.3390/cimb47090716

[24] Bhutani, V., Varzideh, F., Wilson, S., Kansakar, U., Jankauskas, S. S., & Santulli, G. (2025).

Doxorubicin-Induced Cardiotoxicity: A Comprehensive Update. Journal of cardiovascular development and disease, 12(6), 207. https://doi.org/10.3390/jcdd12060207

[25] Avendaño-Briseño, K. A., Escutia-Martínez, J., Hernández-Cruz, E. Y., & Pedraza-Chaverri, J. (2025). Antioxidant Effect of Curcumin and Its Impact on Mitochondria: Evidence from Biological Models. Journal of xenobiotics, 15(5), 139. https://doi.org/10.3390/jox15050139

[26] Pugazhendhi, A.; Edison, T.N.J.I.; Velmurugan, B.K.; Jacob, A.J.; Karuppusamy, I. Toxicity of Doxorubicin (Dox) to different experimental organ systems. Life Sci. 2018, 200, 26–30. [CrossRef]

[27] Siswanto, S.; Arozal, W.; Juniantito, V.; Grace, A.; Agustini, F.D.; Nafrialdi. The effect of mangiferin against brain damage caused by oxidative stress and inflammation in- duced by doxorubicin. HAYATI J. Biosci. 2016, 23, 51–55. [CrossRef]

[28] Oleaga, C.; Bernabini, C.; Smith, A.S.; Srinivasan, B.; Jackson, M.; McLamb, W.; Platt, V.; Bridges, R.; Cai, Y.; Santhanam, N.; et al. multi-Organ toxicity demonstration in a functional human in vitro system composed of four organs. Sci. Rep. 2016, 6, 20030. [CrossRef] [PubMed]

[29] Liu, Z., Huang, P., Law, S., Tian, H., Leung, W., & Xu, C. (2018). Preventive Effect of Curcumin Against Chemotherapy-Induced Side-Effects. Frontiers in pharmacology, 9, 1374. https://doi.org/10.3389/fphar.2018.01374

[30] Sharifi-Rad, J., Rayess, Y. E., Rizk, A. A., Sadaka, C., Zgheib, R., Zam, W., Sestito, S., Rapposelli, S., Neffe-Skocińska, K., Zielińska, D., Salehi, B., Setzer, W. N., Dosoky, N. S., Taheri, Y., El Beyrouthy, M., Martorell, M., Ostrander, E. A., Suleria, H. A. R., Cho, W. C., Maroyi, A.Martins, N. (2020). Turmeric and Its Major Compound Curcumin on Health: Bioactive Effects and Safety Profiles for Food, Pharmaceutical, Biotechnological and Medicinal Applications. Frontiers in pharmacology, 11, 01021. https://doi.org/10.3389/fphar.2020.01021