Biometals
https://doi.org/10.1007/s10534-025-00703-8

RESEARCH

Biodegradable Mg–Cu alloy inhibits HBV replication and hepatocellular carcinoma progression

Heyu Zheng · Weiping Zhou · Meiqi Mao · Yiwei Wang · Xing Tian · Biao Yang · Lu Zhao · Shu Li · Ye Sun · Zhongjia Jiang · Ronghua Fan · Yuxin Bai · Xuanhe Fu · Ke Yang · Guangyan Liu

Received: 20 February 2025 / Accepted: 23 May 2025

Abstract This study explores the biocompatibility and inhibitory effects of magnesium (Mg) and its alloy, specifically the Mg–Cu alloy, on hepatocellular carcinoma (HCC) cells. The importance of this research stems from the potential use of magnesium alloys as biomaterials in bone repair and tissue engineering, while their effects on cancer cells have not been thoroughly investigated. Existing literature shows that although the degradation properties and biocompatibility of magnesium alloys have been examined, their anticancer properties remain a topic of debate. Thus, this study aims to clarify the impact of the Mg–Cu alloy on HCC cells, providing a theoretical foundation for its use in tumor therapy. We utilized various methods, including sample preparation, cell culture, cell viability assays (CCK8), cell cycle and apoptosis analysis, and luciferase activity

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10534-025-00703-8.

H. Zheng · Y. Wang · L. Zhao
Molecular Morphology Laboratory, School of Basic Medicine, Shenyang Medical College, Shenyang 110034, China

H. Zheng · M. Mao
Department of Pathology and Pathophysiology, School of Basic Medicine, Shenyang Medical College, Shenyang 110034, China

W. Zhou · B. Yang · Y. Sun · Y. Bai · G. Liu (✉)
Department of Pathogen Biology, School of Basic Medicine, Shenyang Medical College, Shenyang 110034, China
e-mail: liuguangyan@symc.edu.cn

Y. Wang · L. Zhao · S. Li · G. Liu
Liaoning Province Key Laboratory of Phenomics of Human Ethnic Specificity and Critical Illness, Shenyang Medical College, Shenyang 110034, China

Y. Wang · L. Zhao · S. Li · G. Liu
Shenyang Key Laboratory of Phenomics, Shenyang Medical College, Shenyang 110034, China

X. Tian
Department of Physiology, School of Basic Medicine, Shenyang Medical College, Shenyang 110034, China

S. Li
Department of Histology and Embryology, School of Basic Medicine, Shenyang Medical College, Shenyang 110034, China

Z. Jiang
Department of Biochemistry and Molecular Biology, School of Basic Medicine, Shenyang Medical College, Shenyang 110034, China

R. Fan
Department of Sanitary Inspection, School of Public Health, Shenyang Medical College, Shenyang 110034, China

X. Fu
Department of Immunology, School of Basic Medicine, Shenyang Medical College, Shenyang 110034, China

Published online: 14 June 2025

detection, to comprehensively evaluate the effects of magnesium and its alloys on cellular behavior. Our findings indicate that the Mg–Cu alloy significantly reduces the viability of HCC cells–Huh7 and enhances apoptosis, with a pronounced effect noted at higher extract concentrations. Additionally, the Mg–Cu alloy effectively inhibits hepatitis B virus (HBV) replication, suggesting its potential as an antiviral agent. In summary, this study highlights the promising anticancer and antiviral properties of the Mg–Cu alloy, indicating its potential applications in biomedical fields. Future research should concentrate on the clinical implications and the mechanisms that underlie these effects.

Keywords Hepatocellular carcinoma · Hepatitis B virus · Magnesium alloy · Magnesium copper alloy · Biodegradable

Introduction

Hepatocellular carcinoma (HCC) constitutes 90% of the live cancer, which is a major health problem with approximating 850,000 cases annually, and is the second leading cause of cancer-related mortality around the world (Forner et al. 2018). The estimated deaths of men are the fifth leading cause, but the seventh one in women, in the United State according to the 2023 cancer statistics (Siegel et al. 2023). Hepatitis B virus (HBV) is the main cause of the viral hepatitis related HCC. There are more than 240 million people are suffering chronic HBV infections, which may develop into liver cirrhosis or HCC with the progression of the disease (Revill et al. 2019). A series of advances have been used in the clinical treatment of HCC, but the five-year survival rate of patients with HCC is still very low. Therefore, a new clinical strategy for treating HCC and inhibiting its proliferation should be urgently explored.

Magnesium (Mg) and its alloys have shown unique biodegradability, good mechanical properties, and excellent biocompatibility, demonstrating great potentials in the medical field (Zhao et al. 2019) such as orthopaedic fixation, cardiovascular scaffolds, and resorbable implants (Delavar et al. 2023, Xing et al. 2022, Zhang et al. 2022). For the tumor suppression, recent advancements on Mg-based alloy are mainly associated with the products of their degradation (Yang et al. 2022; Globig et al. 2023; Qiao et al. 2020). However, the degradation rate of pure magnesium is too fast, the mechanical properties (e.g., strength, ductility) are insufficient, and the degradation process may generate hydrogen accumulation, which limits its clinical applications. In order to optimise the overall performance of magnesium alloys, researchers usually add different elements (e.g. zinc, calcium, rare earth elements, etc.) by means of alloying to modulate their degradation behaviour, mechanical properties and biosafety (Pogorielov et al. 2017). Copper (Cu), a trace element with broad-spectrum antimicrobial and pro-angiogenic functions, has been introduced into magnesium alloy systems to simultaneously enhance their corrosion resistance, mechanical properties, and bioactivity (Liu et al. 2016; Zhao et al. 2020; Yan et al. 2018). Studies have shown that the addition of appropriate amount of Cu can refine the grain structure of magnesium alloys and improve their strength and ductility; at the same time, the slow release of Cu can endow the alloys with long-lasting antimicrobial ability and reduce the risk of post-implantation infection. In addition, Cu ions can promote the proliferation of endothelial cells during the degradation process and accelerate tissue repair. However, excessive Cu may lead to cytotoxicity or accelerated corrosion, so its content and distribution need to be precisely regulated. In this paper, we systematically explore the effects of microstructure, degradation behaviour, mechanical properties and biocompatibility of Mg–Cu alloys, and look forward to its future optimization direction, which is of great significance for the development of new magnesium alloys with excellent mechanical properties, controlled degradation and multifunctional bioactivity.

A strong interaction between the material and carcinoma may provide a new way to treat HCC. Previously, it was reported that the Cu levels increased in the tumor patients (Babak and Ahn 2021), which could play a vital role of antitumor effect. Cu could

K. Yang (✉)
Institute of Metal Research, Chinese Academy of Sciences, 72 Wenhua Road, Shenyang 110016, China
e-mail: kyang@imr.ac.cn

G. Liu
Key Laboratory of Environment Pollution and Microecology of Liaoning Province, Shengyang Medicial College, Shenyang 110034, China

induce the cell death dependent on the mitochondrial respiration by targeting lipoylated tricarboxylic acid cycle proteins (Tsvetkov et al. 2022). Cu and cuproptosis-related genes were also found to be related to the development of HCC by targeting the tumor immune microenvironments and immune checkpoint genes (Wang et al. 2023). Low levels of Mg occurred in the HCC patients with nonalcoholic fatty liver disease, and were significantly associated with the decreased risk of HCC (Yu et al. 2023). Liu et al. found that Mg demethylcantharidate inhibited HCC cell invasion and metastasis via activation transcription factor FOXO1 (Liu et al. 2021). Therefore, both Cu and Mg separately showed the effect of anti-tumor, but how the effect a biodegradable Mg–Cu alloy is on HCC is not clear.

In this study, a biodegradable Mg–Cu alloy was used to explore its effect on the HCC development, and it was found that the Mg–Cu alloy could inhibit the hepatocytes proliferation and the promote related apoptosis. Furthermore, the Mg–Cu alloy showed inhibition to HBV replication. This study demonstrates that Mg–Cu alloy may provide a potential treatment strategy for HCC.

Materials and methods

Sample preparation and soaking experiment

Pure Mg and a Mg–0.2wt.% Cu (Mg–Cu) alloy were melted and cast into cylindrical billets with a diameter of 10 mm, which were then cut into ø 10 × 3 mm discs. After cleaning and ultraviolet (UV) treatment, the samples were immersed in DMEM medium containing 10% FBS, with a ratio of medium volume to sample surface area of 1 mL:1.25cm^2. The samples were maintained with DMEM in an incubator with 5% CO_2 at 37 °C for 6, 12, 18, 24, 48 and 72 h, respectively. All samples with various immersion times were draw out for cleaning in chromic acid following by rinsing with anhydrous ethanol to let them dry. The soaking solutions were collected, and their pH were measured. Surface morphology of the samples was observed under a scanning electron microscope (SEM), and the corresponding corrosion rate was calculated by the weight loss.

Cell culture

Cells (Huh7 and HEK-293 T cells) were maintained in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS), penicillin (100 IU/ml) and streptomycin (100 mg/ml), which were incubated at 37 ℃ with 5% CO_2.

Sample extracts preparation

Different grade of sandpapers were used to burnish pure Ti (as a contract in this study), Mg and Mg–Cu alloy until achieving a smooth surface. Further, high pressure and ultraviolet were applied to treat the above materials for sterilization. The samples of Ti, Mg and Mg–Cu alloy were put in the solution of 10% FBS, penicillin (100 IU/ml) and streptomycin (100 mg/ml) containing DMEM medium with a ratio of medium volume to sample surface area of 1 mL:1.25 cm^2. Then their supernatants were collected after 24 h cells incubation (stocking fluid concentration was 100%), respectively.

CCK8

Cells were added into the above extracts, and their OD values were detected according to the manufacture instructions (Biosharp) after 48 h co-cultures, respectively.

Cell cycle

Cells were added into the above extracts. Cells were collected after 48 h co-culture with sample extracts, then were examined according to the cell cycle and apoptosis detection kit instruction (Beyotime Biotech. Co., China, C1052). The cell cycle test was performed immediately by Accuri™ C6 Plus (BD, America).

Cell apoptosis

Cells were treated by the above extracts for 48 h. The manipulate was carried out according to the Annexin V-FITC/PI double staining apoptosis detection kit (Keygen Biotech. Co., China, KGA1102). The Accuri™ C6 Plus (BD, America) was immediately applied to measure the apoptosis rate.

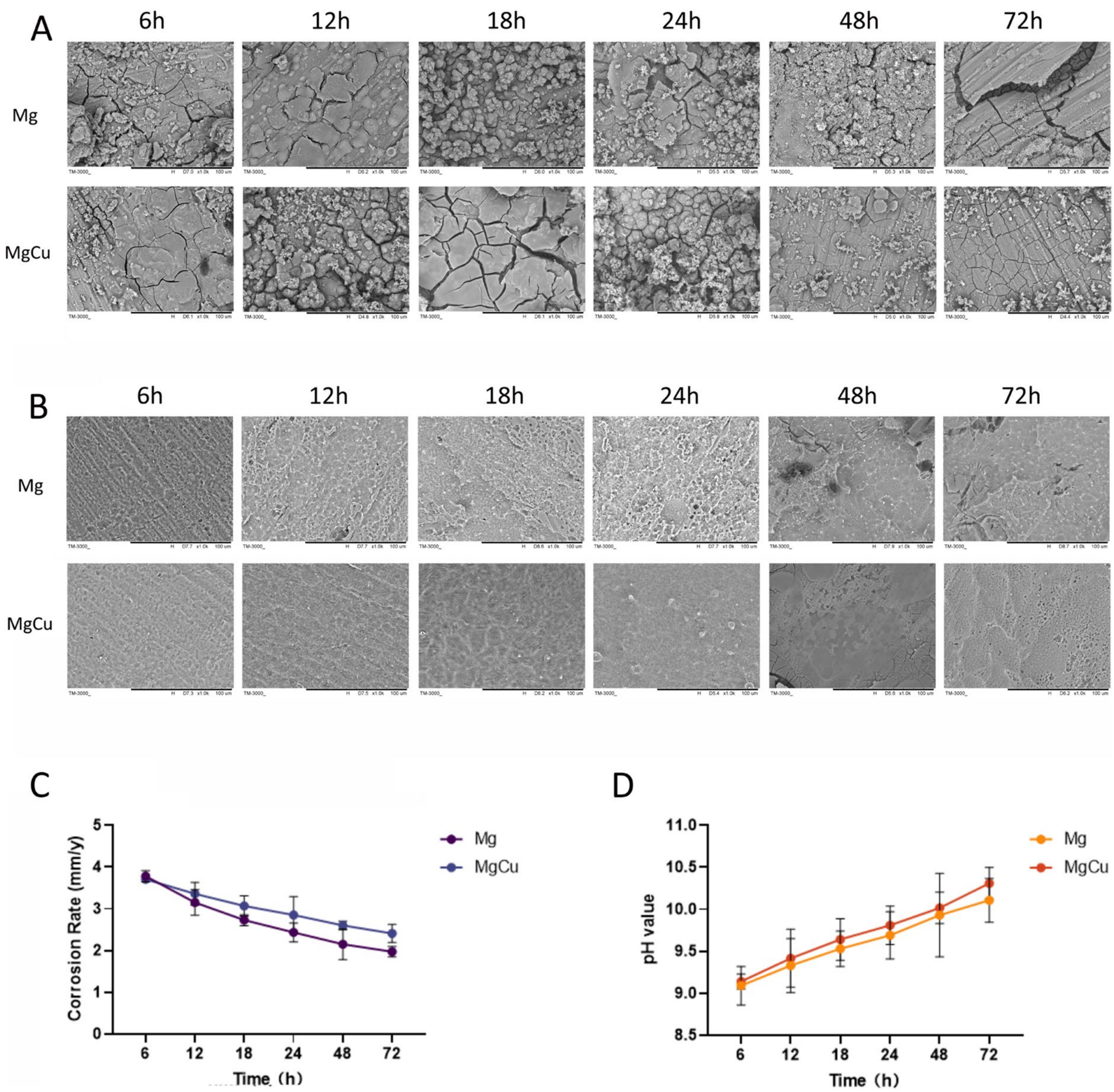


Fig. 1 Degradation characteristics of Mg and Mg–Cu alloy. Scanning electron microscope (SEM) was used to observe the degradation morphology (**A**) and corrosion pits (**B**) on the Mg and Mg–Cu alloy. As extension of the immersion time, the changes of degradation rates (**C**) and pH value (**D**) were evaluated

Luciferase assay

Cells were transfected with the pCMV1.2xHBV/NL reported plasmids with lipofectamine 2000 (Invitrogen, USA, 11668019). Afte 72 h transfection, the cells were lysed with passive lysis buffer, and then nano-luciferase activity was measured by the Nano-Glo® Luciferase Assay System (N1120, Promega). The procedures were described previously (Que et al. 2017).

Statistical analysis

GraphPad Prism 9 software (GraphPad Software, San Diego, CA) and two-tailed Student's *t* test were used for data analysis. All data are presented as the

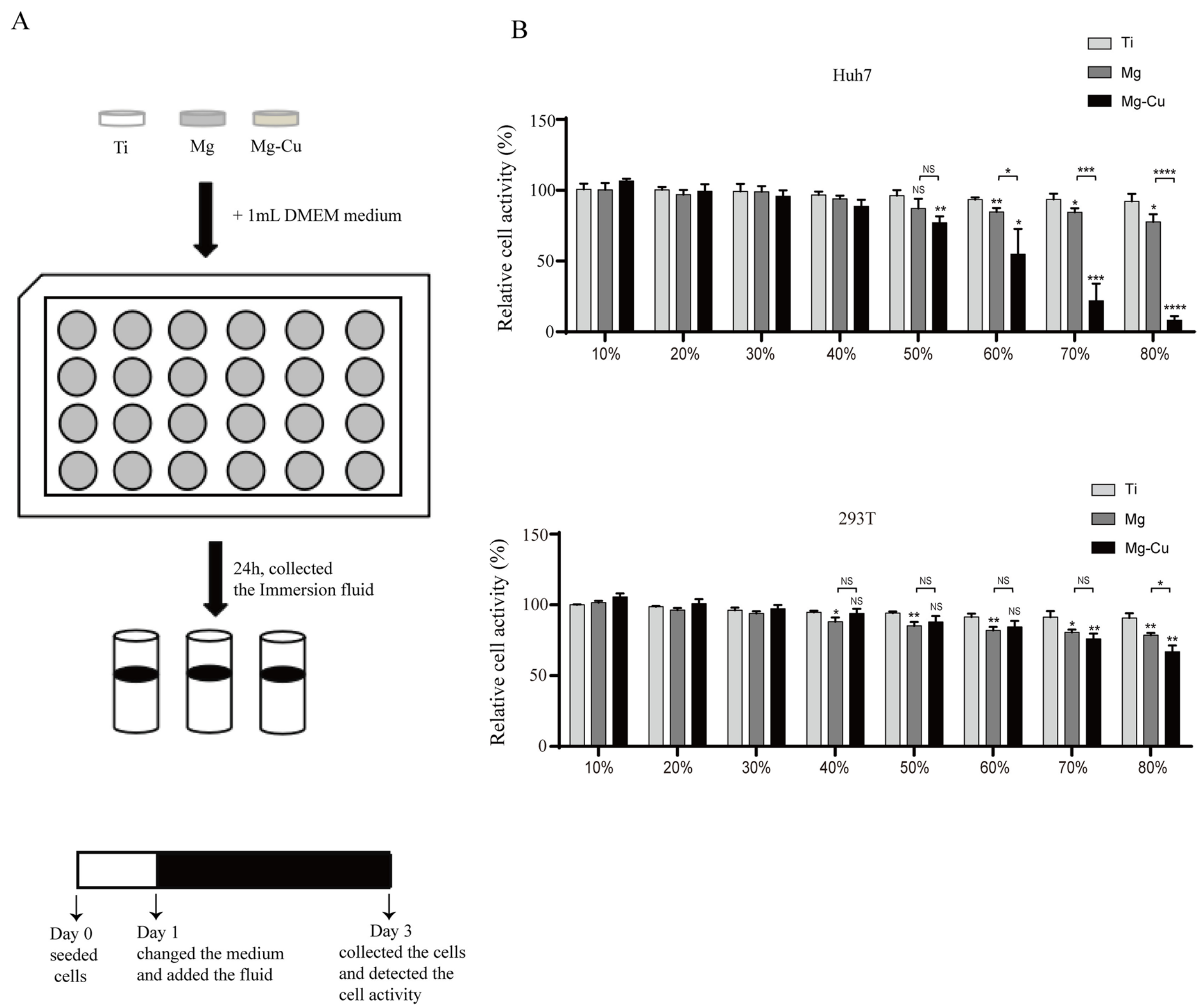


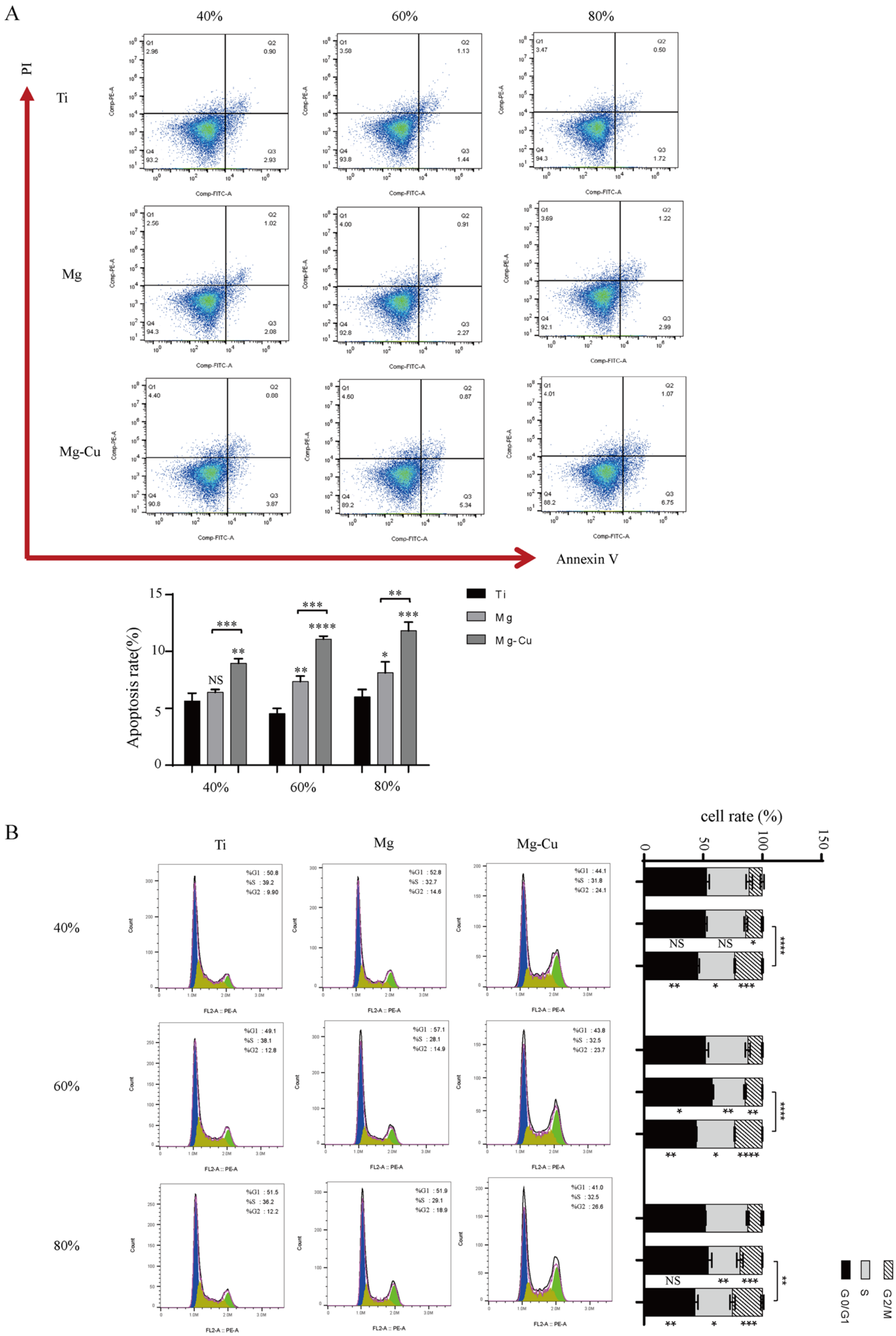
Fig. 2 Mg and Mg–Cu alloy suppressing the cell proliferation. **A** Schematic illustrations of Ti, Mg and Mg–Cu alloy extracts were acquired with DMEM medium treatment. **B** Extracts of Ti, Mg and Mg–Cu alloy were applied to treat Huh7 and HEK-293T cells for 48 h, CCK8 was used to detect the activity of cell proliferation. The cell activity of 10% Ti extract is defined as value 100%. N = 3, NS, not significant; $*p<0.05$, $**p<0.01$, $***p<0.001$, $****p<0.0001$

mean ± S.D. Significant difference was defined as $p<0.05$.

Results

Degradation characteristics

The degradation morphologies of Mg and Mg–Cu alloy were studied through SEM observation. All sample surfaces showed corrosion (i.e., degradation) behavior with different degree after immersion in the cell culture media (DMEM) for 6, 12, 18, 24, 48 and 72 h, respectively (Fig. 1A). Furthermore, the surface corrosion products were removed by chromic acid. The corrosion pits on the surfaces of Mg and Mg–Cu alloy were observed, more uniform on Mg–Cu alloy than on Mg (Fig. 1B). In addition, the degradation rate decreased and the pH value gradually increased as extension of the immersion time for both Mg and Mg–Cu alloy (Fig. 1C, D). And it was proved through EDS and XRD experiments that in the Mg—0.2wt.%Cu alloy, Cu exists in the form of the Mg_2Cu second phase (Figures S1 and S2).


A
40%
60%
80%
PI
Ti
Mg
Mg-Cu
Annexin V
Apoptosis rate(%)
Ti
Mg
Mg-Cu
B
Ti
Mg
Mg-Cu
40%
60%
80%
cell rate (%)
G 0/G1
S
G2/M

◂**Fig. 3** Mg and Mg–Cu alloy promoting the cell apoptosis. **A** Effect of different concentrations of Ti, Mg or Mg–Cu alloy extracts on the apoptosis of Huh7 cells. **B** Effect of different concentrations of Ti, Mg or Mg–Cu alloy extracts on the cell cycle of Huh7 cells. N = 3, NS, not significant; $*p<0.05$, $**p<0.01$, $***p<0.001$, $****p<0.0001$

Carcinoma cells viability

The inhibitory effects of Mg and Cu on HCC have been reported, but whether the Mg–Cu alloy has such effect is not clear. Firstly, extracts of Ti, Mg and Mg–Cu alloy (Figure S3) were collected and applied to treat the cells for 48 h (Fig. 2A). The cell viability of Huh7 and HEK-293 showed that Mg and Mg–Cu alloy could inhibit the cell activity significantly with increasing the concentration of corresponding extract, but inhibitory effect of Ti extract (control group) on the cells was not obvious (Fig. 2B top). Meanwhile, Mg–Cu alloy exhibited about 25 and 80% inhibitory effects on Huh7 cells with 50 and 70% extracts, respectively. In contrast, Mg exhibited about 15 and 20% inhibitory effects on Huh7 cells by the 60 and 70% extracts, respectively. Moreover, Mg–Cu alloy had a little effect (about 25%) on HEK-293 T cells at 70% extract concentration (Fig. 2B). These results demonstrates that both Mg and Mg–Cu alloy suppressed activities of the cellular carcinoma cells, but Mg–Cu alloy expressed more significant inhibitory effect and limited influence on normal cells.

Cell apoptosis

As shown in Fig. 3A, the cell apoptosis rate increased with concentration of Mg and Mg–Cu alloy extracts, compared with the Ti group (control group). Interestingly, Mg–Cu alloy showed much high apoptosis in the 40% concentration, while Mg could not. The cell cycle showed the consistent results with the cell apoptosis (Fig. 3B). Briefly, the ratios of G2/M phase of Mg–Cu alloy group accounted for more than the Mg group with increasing the concentration, and the proportion of G0/G1 phases of Mg–Cu alloy group decreased more than the Mg group. These exhibits that both Mg and Mg–Cu alloy, compared with Ti, could promote the cell apoptosis, and the role of Mg–Cu alloy was stronger.

Inhibitory roles on HBV replication

HBV infection is closed to the HCC development. When the extract concentration was less than 30%, neither Mg nor Mg–Cu alloy affected the cells significantly (Fig. 2). Thus the above mentioned Ti, Mg and Mg–Cu alloy were examined to verify their impact on HBV replication under 30% concentration of the extract The pCMV1.2 × HBV/NL plasmid is a reporting system for HBV pre-genomic RNA (pgRNA), and luciferase signal value represents the level of HBV pgRNA. The luciferase assay displayed that Mg–Cu alloy, instead of Ti and Mg, suppressed the nanoluciferase activity of HBV markedly, as increasing the the extract concentration (Fig. 4). This suggests that only Mg–Cu alloy with Cu addition could inhibit the HBV transcript level.

Discussion

The corrosion behaviour of magnesium (Mg) and its alloys is closely related to their biocompatibility, and the mechanism of this correlation is particularly critical in the antitumour and antiviral applications of Mg–Cu alloys. Firstly, the degradation rate of the alloy directly affects the pH and ion concentration of the local microenvironment. In this study, the degradation rate of Mg and Mg–Cu alloys gradually decreased with the prolongation of immersion time, while the pH increased (Fig. 1C, D), forming an alkaline microenvironment. High pH may inhibit cells, but excessive alkalinity (pH > 10.5) may be toxic to normal cells. However, the buffering capacity of body fluids in physiological environments can partially neutralise the pH mutation and thus reduce the damage to tissues (Liu et al. 2016; Zhao et al. 2020; Yan et al. 2018). SEM observations showed that the corrosion pit distribution of Mg–Cu alloys was more homogeneous than that of pure Mg (Fig. 1B), suggesting that the incorporation of Cu improved the corrosion homogeneity of the alloys and reduced the toxicity of the localised areas of high ion concentration to normal cells. In addition, the Cu^{2+} released during degradation has an antiviral effect. Mg–Cu alloys inhibit the transcription of HBV pregenomic RNA (pgRNA) by suppressing the transcription of HBV (Fig. 4), which may be related to the mechanism by which its degradation product directly interferes with

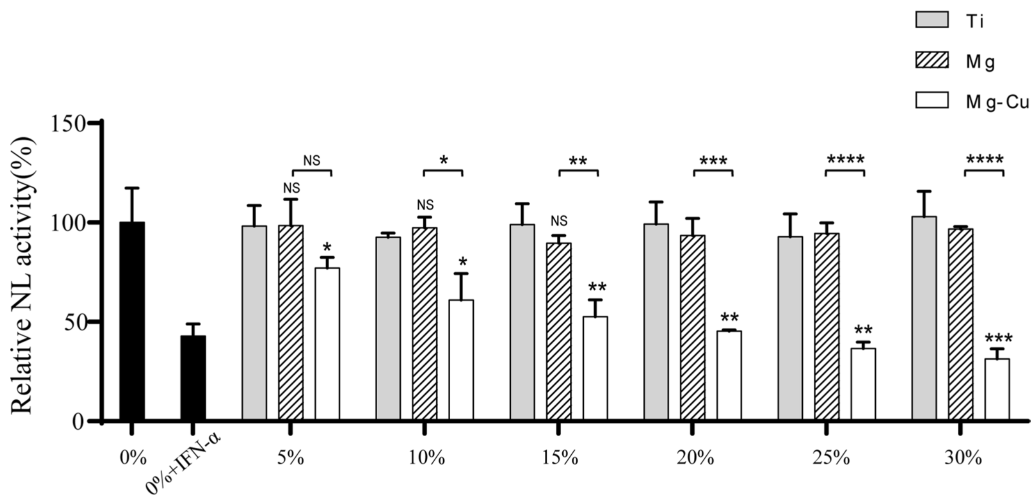


Fig. 4 Mg–Cu alloy blocking the HBV replication. Huh7 cells were transfected with the pCMV1.2xHBV/NL reported plasmid, and different indicated concentrations of Ti, Mg or Mg–Cu alloy extracts were cultured. The nano-luciferase values were acquired with Nano-Glo® Luciferase Assay System and the NL activities of untreated samples are defined as value 100%. N = 3, NS, not significant; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$

viral replication or blocks viral entry into the host cell (Bhatti and DeLong 2023). This dual function (anticancer and antiviral) further highlights the synergistic effect of corrosion behaviour and biocompatibility.

The therapeutic effect of metal materials on HCC gradually come into sight. Both pure Mg and Mg–Cu alloy could inhibit the HCC proliferation and promote the cell apoptosis, and Mg–Cu alloy exhibited stronger influence. Further, Mg–Cu alloy could significantly inhibit the cells viability at a relative low concentration (50%), but not Mg alone or HEK-293T cells, which reveals higher potential of Mg–Cu alloy for clinical practice with less influence on the normal cells. Mg–Cu alloy has shown to possess a long-lasting antibacterial effect(Liu et al. 2016), which manifests that Mg–Cu alloy is also against the bacterial infection when it is used for surgical treatment of HCC. Meanwhile, Mg–Cu alloy might attenuate the HBV replication, which is important for preventing the occurrence of HCC resulting from HBV infection. All of these illustrate that Mg–Cu alloy should be a more ideal anti-cancer material, especially to the HBV associated HCC. Therefore, the above results and the related mechanisms about inhibitory effect of Mg–Cu alloy on both HCC and HBV need to be further discussed.

Mg can suppress the carcinoma development mainly through four aspects: (1) excessive Mg can increase the cancer metabolism; (2) more Mg results in hypo phosphorylation; (3) Mg reduces p38/MPK signaling pathway activity to cause abnormal cell differentiation; (4) excess Mg results in p53 inactivation and cancer progression (Ashique et al. 2023). Cu can participate in multiple processes of HCC, including hepatocarcinogenesis, angiogenesis, metastasis, and antitumor immune response. The roles of Cu in HCC should show a double-edged sword: (1) high Cu can enhance the HCC development through stimulating reactive oxygen species (ROS) production, genomic instability, pro-angiogenesis, and pro-tumor signals; (2) but excessive Cu can result in an opposite function: inducing the cell death via apoptosis, paraptosis, pyroptosis, ferroptosis, cuproptosis (Wu et al. 2023). All of these define that both Mg and Cu play inhibitory roles in HCC progression, and the associated mechanisms of Mg–Cu alloy on HCC can be further analyzed based on the above possible mechanisms.

With development of the disease, HBV infection may develop into liver cirrhosis or HCC (Revill et al. 2019). Therefore, it may provide a new way for preventing viral infection or target therapeutic HBV replication by using the Mg–Cu alloy treatment. Nanomaterials have now been found applications for antivirus. Cu, and the oxides including zinc oxide, titanium oxide, iron oxide belong to antiviral nanoparticles, which exhibit the antiviral roles through four major mechanisms: (1) direct viral interaction, (2) interaction to receptor or cell surface to prevent the virus from entering the host cells, (3) suppressing the replication of the virus, or (4) other processing mechanisms which inhibit the spread of virus (Bhatti and DeLong 2023). Therefore, the inhibitory effect and the related mechanisms of Mg–Cu alloy on HBV replication can be further verified in the future based on these aspects.

Collectively, both Mg and Mg–Cu alloy impaired the HCC proliferation and enhanced the cell apoptosis, but Mg–Cu alloy had more prominent. Moreover, Mg–Cu alloy showed a suppressing effect on HBV replication. All of these will facilitate the development of therapeutic agents for the treatment of patients with HBV infection or HCC, and Mg–Cu alloy is expected to serve as a useful material drug.

Conclusions

In conclusion, our study provides compelling evidence that Mg and Mg–Cu eluates possess significant anti-cancer properties by inhibiting the growth of hepatocytes and inducing apoptosis. This novel approach highlights the potential ability of these materials in cancer therapy, particularly in relation to hepatocellular carcinoma (HCC). Furthermore, we have uncovered for the first time that Mg–Cu eluates inhibit the replication of Hepatitis B Virus (HBV). This finding is particularly significant, as HBV is known to play a critical role in the pathogenesis of HCC, thus establishing a dual mechanism through which Mg–Cu can exert its beneficial effects.

Acknowledgements The study was financially supported by Team Construction Project of Liaoning Province Education Department (LJ222410164013), the Natural Science Foundation of Liaoning Province of China (2024010751-JH3/107, 2024-BS-278), Foundation of Liaoning Educational Committee (JYTMS20231388), Liaoning Province Science and Technology Plan Joint Natural Science Foundation (2024011894-JH4/4800), Liaoning Province Science and Technology plan joint plan (2024-MSLH-457), and Shenyang Medical College Master's Student Science and Technology Innovation Fund (No.: Y20240507)

Author contributions K.Y. and G.L. designed research; H.Z., Y.W., B.Y., Y.S., L.Z. and W.Z. performed the experiments; Z.J., R.F., Y.B., X.F., G.L., S.L. M.M. and W.Z. analyzed the data; H.Z., Y.W., X.T., K.Y. and G.L. wrote and revised the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

References

Ashique S, Kumar S, Hussain A, Mishra N, Garg A, Gowda BHJ, Farid A, Gupta G, Dua K, Taghizadeh-Hesary F (2023) A narrative review on the role of magnesium in immune regulation, inflammation, infectious diseases, and cancer. J Health Popul Nutr 42(1):74. https://doi.org/10.1186/s41043-023-00423-0

Babak MV, Ahn D (2021) Modulation of intracellular copper levels as the mechanism of action of anticancer copper complexes: clinical relevance. Biomedicines 9(8):852. https://doi.org/10.3390/biomedicines9080852

Bhatti A, DeLong RK (2023) Nanoscale interaction mechanisms of antiviral activity. ACS Pharmacol Transl Sci 6(2):220–228. https://doi.org/10.1021/acsptsci.2c00195

Delavar H, Mostahsan AJ, Ibrahim H (2023) Corrosion and corrosion-fatigue behavior of magnesium metal matrix composites for bio-implant applications: a review. J Magnes Alloys 11(4):1125–1161. https://doi.org/10.1016/j.jma.2023.04.010

Forner A, Reig M, Bruix J (2018) Hepatocellular carcinoma. Lancet (London, England) 391(10127):1301–1314. https://doi.org/10.1016/s0140-6736(18)30010-2

Globig P, Madurawala R, Willumeit-Römer R, Martini F, Mazzoni E, Luthringer-Feyerabend BJC (2023) Mg-based materials diminish tumor spreading and cancer metastases. Bioactive Mater 19:594–610. https://doi.org/10.1016/j.bioactmat.2022.05.002

Liu C, Fu X, Pan H, Wan P, Wang L, Tan L, Wang K, Zhao Y, Yang K, Chu PK (2016) Biodegradable Mg-Cu alloys with enhanced osteogenesis, angiogenesis, and long-lasting antibacterial effects. Sci Rep 6:27374. https://doi.org/10.1038/srep27374

Liu F, Zhu XT, Li Y, Wang CJ, Fu JL, Hui J, Xiao Y, Liu L, Yan R, Li XF, Liu Y (2021) Magnesium demethylcantharidate inhibits hepatocellular carcinoma cell invasion and metastasis via activation transcription factor FOXO1. Eur J Pharmacol 911:174558. https://doi.org/10.1016/j.ejphar.2021.174558

Pogorielov M, Husak E, Solodivnik A, Zhdanov S (2017) Magnesium-based biodegradable alloys: degradation, application, and alloying elements. Interv Med Appl Sci 9(1):27–38. https://doi.org/10.1556/1646.9.2017.1.04

Qiao S, Wang Y, Zan R, Wu H, Sun Y, Peng H, Zhang R, Song Y, Ni J, Zhang S, Zhang X (2020) Biodegradable Mg implants suppress the growth of ovarian tumor. ACS

Biomater Sci Eng 6(3):1755–1763. https://doi.org/10.1021/acsbiomaterials.9b01703

Que L, Liu G, Kitamura K, Wakae K, Li Y, Nishitsuji H, Ujino S, Shimotohno K, Muramatsu M (2017) Molecular characterization of AID-mediated reduction of hepatitis B virus transcripts. Virology 510:281–288. https://doi.org/10.1016/j.virol.2017.07.035

Revill A, Chisari FV, Block JM, Dandri M, Gehring AJ, Guo H, Hu J, Kramvis A, Lampertico P, Janssen HLA, Levrero M, Li W, Liang TJ, Lim SG, Lu F, Penicaud MC, Tavis JE, Thimme R, I.C.E.H.B.V.W.G. Members of the, I.-H.S.G. Chairs, I.-H.S. Advisors, Zoulim F (2019) A global scientific strategy to cure hepatitis B. Lancet Gastroenterol Hepatol 4(7):545–558. https://doi.org/10.1016/S2468-1253(19)30119-0

Siegel RL, Miller KD, Wagle NS, Jemal A (2023) Cancer statistics, 2023. CA Cancer J Clin 73(1):17–48. https://doi.org/10.3322/caac.21763

Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, Rossen J, Joesch-Cohen L, Humeidi R, Spangler RD, Eaton JK, Frenkel E, Kocak M, Corsello SM, Lutsenko S, Kanarek N, Santagata S, Golub TR (2022) Copper induces cell death by targeting lipoylated TCA cycle proteins. Science 375(6586):1254–1261. https://doi.org/10.1126/science.abf0529

Wang X, Chen D, Shi Y, Luo J, Zhang Y, Yuan X, Zhang C, Shu H, Yu W, Tian J (2023) Copper and cuproptosis-related genes in hepatocellular carcinoma: therapeutic biomarkers targeting tumor immune microenvironment and immune checkpoints. Front Immunol 14:1123231. https://doi.org/10.3389/fimmu.2023.1123231

Wu Z, Lv G, Xing F, Xiang W, Ma Y, Feng Q, Yang W, Wang H (2023) Copper in hepatocellular carcinoma: a double-edged sword with therapeutic potentials. Cancer Lett 571:216348. https://doi.org/10.1016/j.canlet.2023.216348

Xing F, Li S, Yin D, Xie J, Rommens PM, Xiang Z, Liu M, Ritz U (2022) Recent progress in Mg-based alloys as a novel bioabsorbable biomaterials for orthopedic applications. J Magnes Alloys 10(6):1428–1456. https://doi.org/10.1016/j.jma.2022.02.013

Yan X, Wan P, Tan L, Zhao M, Qin L, Yang K (2018) Corrosion and biological performance of biodegradable magnesium alloys mediated by low copper addition and processing. Mater Sci Eng C 93:565–581. https://doi.org/10.1016/j.msec.2018.08.013

Yang N, Gong F, Liu B, Hao Y, Chao Y, Lei H, Yang X, Gong Y, Wang X, Liu Z, Cheng L (2022) Magnesium galvanic cells produce hydrogen and modulate the tumor microenvironment to inhibit cancer growth. Nat Commun 13(1):2336. https://doi.org/10.1038/s41467-022-29938-6

Yu YC, Paragomi P, Wang R, Liang F, Luu HN, Behari J, Yuan JM (2023) High serum magnesium is associated with lower risk of hepatocellular carcinoma among patients with nonalcoholic fatty liver disease. Cancer 129(15):2341–2347. https://doi.org/10.1002/cncr.34799

Zhang T, Wang W, Liu J, Wang L, Tang Y, Wang K (2022) A review on magnesium alloys for biomedical applications. Front Bioeng Biotechnol 10:953344. https://doi.org/10.3389/fbioe.2022.953344

Zhao Y, Chen X, Li S, Zeng R, Zhang F, Wang Z, Guan S (2019) Corrosion resistance and drug release profile of gentamicin-loaded polyelectrolyte multilayers on magnesium alloys: effects of heat treatment. J Colloid Interface Sci 547:309–317. https://doi.org/10.1016/j.jcis.2019.04.017

Zhao X, Wan P, Wang H, Zhang S, Liu J, Chang C, Yang K, Pan Y (2020) An antibacterial strategy of Mg-Cu bone grafting in infection-mediated periodontics. BioMed Res Int 2020(1):7289208. https://doi.org/10.1155/2020/7289208