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A REVIEW ON THE EPIGENETICS MODIFICATIONS TO NANOMATERIALS IN HUMANS AND ANIMALS: NOVEL EPIGENETIC REGULATOR

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Abstract

In the nanotechnology era, nanotechnology applications have been intensifying their prospects to embrace all the vigorous sectors persuading human health and animal. The safety and concerns regarding the widespread use of engineered nanomaterials (NMs) and their potential effect on human health still require further clarification. Literature elucidated that NMs exhibited significant adverse effects on various molecular and cellular alterations. Epigenetics is a complex process resulting in the interactions between an organism's environment and genome. The epigenetic modifications, including histone modification and DNA methylation, chromatin structure and DNA accessibility alteration, regulate gene expression patterns. Disturbances of epigenetic markers induced by NMs might promote the sensitivity of humans and animals to several diseases. Also, this paper focuses on the epigenetic regulators of some dietary nutrients that have been confirmed to stimulate the epigenome and, more exactly, DNA histone modifications and non-histone proteins modulation by acetylation, and phosphorylation inhibition, which counteracts oxidative stress generations. The present review epitomizes the recent evidence of the potential effects of NMs on histone modifications, in addition to *in vivo* and *in vitro* cytosine DNA methylation and its toxicity. Furthermore, the part of epigenetic fluctuations as possible translational biomarkers for uncovering untoward properties of NMs is deliberated.

Key words: epigenetics modifications, nanomaterials, humans, animals, regulators

Recently, nanotechnology has received substantial attention and has stretched to various fields in our life and environment (Gupta and Xie, 2018). Ten thousand commercial nanoparticle products have been created and developed for their application in several purposes, including medicine, water bioremediation, food and cosmetic products, drug delivery, and agricultural uses (Ghosh et al., 2022). The coating forms of silica (SDNPs) and titanium (TDNPs) dioxide nanoparticles have been employed in medical products, agricultural, industrial protection products and cosmetics (Kiany et al., 2022). Other nanomaterials such as carbon nanotubes (CNt) and graphene (GN) nanoparticles are common in structural fiber uses and sportive equipment due to their high intrinsic mechanical features, little densities, and high electrical /thermal conductivities (Eom et al., 2021).

While the nanoparticles of rhodium, cerium oxide, palladium, and platinum, are involved in vehicle catalytic convertors to decrease detrimental automobile exhaust. Because of the powerful antimicrobial properties of copper nanoparticles (CuNPs) and silver nanoparticles (AgNPs), they are commonly used in clothes, bedsheets, towels, and carpets (Gharpure et al., 2020). As a result of the extensive usage of nanomaterials (NMs) in several

fields, humans and animals are exposed to those NMs, so it is interesting to study the potential effects of nanomaterials on animal and human health.

Consequently, over the last decades, the biological properties of nanomaterials and their toxicological effects have been extensively examined and they are still investigated (Shyamasundar et al., 2015; Missaoui et al., 2018; Ameh and Sayes, 2019; Schulte et al., 2019; Xiaoli et al., 2020). Nevertheless, the consequence of NMs on the epigenome is an emerging area with inconclusive and restricted data in the area of nanotoxicological research and various unanswered questions (Shyamasundar et al., 2015; Sierra et al., 2016). The impacts of several NMs exposure on two main epigenetic mechanisms, histone modifications and DNA methylation, and the possible role of epigenetic variations in the nanomaterial's toxicity mechanisms are summarized in this review article.

DNA methylation

The methylation of DNA is one of the most considered alterations of epigenetics constituents. In addition, it is a hereditary epigenetic spot relating the covalent transfer of a methyl group to the C-5 position of the cytosine ring of DNA via DNA methyltransferases (DNMT) (Figure 1). This previous process can lead to 5-methylcytosine (5-meC) in DNA. Likewise, it is well known as a covalent modulation of DNA cytosine residues. The methylation of DNA is a well-stable process and self-motivated reaction concerning cellular DNA demethylation and the responses of DNA methylation (Ooi et al., 2009). The *de novo* DNA methylation occurs at cytosines of dinucleotides of CpG, where Dnmt3a and Dnmt3b are the enzymes accountable for this action.

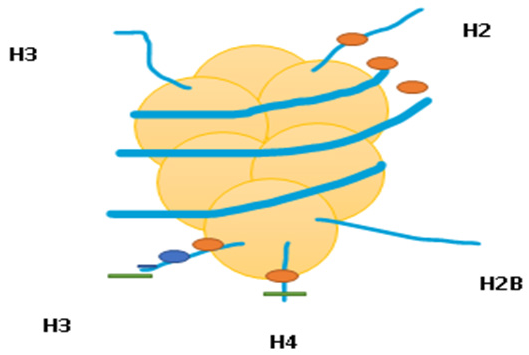

Figure 1. The machinery system of epigenetics includes DNA methylation, acetylation ubiquitination, and phosphorylation. H3, histone 3; H4, histone H4 acetylation; H2B, histone H2B (ubiquitination) in the cellular system

Further, the DNA methyltransferase *DNMT1* conservation sustains it through the replication of DNA (Ooi et al., 2009). This DNA modification is related to several biological events. Scientists suggested that enzymes of the ten-eleven translocation family can catalyze the stepwise oxidation of 5-meC in DNA to 5-hmC and additional oxidation yields, not only causing new epigenetic characters but moreover introducing active or passive demethylation ways (Figure 2) (Wu and Zhang, 2017). The key epigenetic machinery is complicated with an expression of the regulatory gene. DNA methylation consists of adding a methyl group in cytosine in a cytosine–phosphate–guanine (CpG) dinucleotide. This process comprises several vital processes, including methylation, acetylation, and phosphorylation

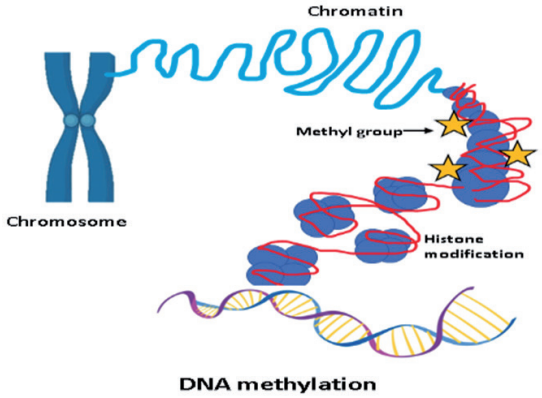

Figure 2. The key epigenetic machinery is complicated with an expression of the regulatory gene. DNA methylation consists of adding a methyl group in cytosine in a cytosine–phosphate–guanine (CpG) dinucleotide. This process comprises several vital processes, including methylation, acetylation, and phosphorylation

Effects on DNA methylation (*in vitro* model)

As mentioned above, several nanomaterials have been explored in *in-vitro* models (Table 1 and Figure 3).

Carbon nanoparticles

Carbon nanoparticles (CNP) have attracted abundant consideration owing to their distinctive structural variety. Multiple authors have reported the potential effects of CNP on *in vitro* models (Sima et al., 2020; Öner et al., 2020). The research conducted by Sima et al. (2020) clarified that exposing human embryonic lung fibroblast (HEL 12469 cells) to different levels of carbon dots for 24 h (with an average of 10–500 µg/mL) did not exhibit a significant influence on the methylation of DNA (Sima et al., 2020).

Carbon nanomaterials have been broadly applied in pharmaceutical sciences for drug delivery, diagnosis, and distinct biological interaction in the past few years. However, until now, their possible toxicity and consequence on the epigenome of organisms have been poorly discovered. Studies have conveyed that of either human THP-1 monocytic cells (Öner et al., 2020) or human 16HBE14 bronchial epithelial cells (Ghosh et al., 2018) exposure to multi-walled (MWCNTs) or single carbon nanotubes (SWCNTs) for 24 h at 25–100 µg/mL could induce considerable hypomethylation of 1127 genes (Öner et al., 2017).

Table 1. Effects of different nanomaterials on DNA methylation (*in vitro* models)

Nanomaterials	Cells	Doses	The main findings	Reference
1	2	3	4	5
SWCNTs, MWCNTs	Human bronchial epithelial cells (16HBE)	25 and 100 µg/mL of CNTs for 24 h	● No significant effect on global DNA methylation (5-mC and 5-hmC). ● Of 2398 genes was altered and induced DNA hypomethylation. ● Some gene-specific DNA methylation was induced, including *SKI, NF1, AKP8L, GSTP1, FOXK2, EIF4E* and *SHROOM2.*	Öner et al., 2018
CNTs	Human monocytes (THP-1) cells	25 and 100 µg/ml CNTs for 24 h	● No significant effect on global DNA methylation (5-mC and 5-hmC). ● It showed a hypomethylation effect induced by NPs (especially in some genes including *WNT5B, PRKCZ, JAK3-STAT6, VEGFA, TF, NAP2K2, AKT1NOTCH1, NOTCH4, SH2D2A, SFRP1, NOSS, STAT5A, FGFR1,* and *MEIS1*).	Öner et al., 2017
SWCNTs and MWCNTs	Human bronchial epithelial cells (16HBE)	0.25 µg/mL of MWCNTs or SWCNTs for one month	● Results showed no modifications in the global DNA methylation (5-mc) were detected in16HBE cells. ● Exposing cells to SWCNT resulted in hypermethylation of KLF3, PRSS3, KLK3, and HPCAL1 genes.	Öner et al., 2020
CNTs: SWCNTs, MWCNTs	Human bronchial epithelial cells 16HBE	25 and 100 µg/mL of SWCNTs and MWCNTs for 24 h	● There were no changes in DNA methylation markers, including 5-mC and 5-hmC. ● SWCNTs induced significant changes in NPAT/ATM, MYO1C, DNMT1, while MAP3K10, HDAC4 were induced by MWCNTs exposure. ● It showed that the differentially methylated for both nanomaterials triggered hypermethylation of ATM/NPAT promoter.	Ghosh et al., 2018
SWCNTs, MWCNTs	Human bronchial epithelial cells 16HBE	25 and 100 µg/mL of SWCNTs and MWCNTs for 24 h	● MWCNTs brought substantial dose-dependent damage to DNA methylation.	Emerce et al., 2019
CDs	Human embryonic lung fibroblasts HEL12469	10–500 µg/mL of negatively or positively charged CDs for 24 h	● No change in the global DNA methylation marker (5-mC).	Sima et al., 2020
Silica nanoparticles (SNPs)	Human bronchial epithelial cells BEAS-2B	5 µg/mL for 30 passages (prolonged exposure)	● Results revealed that the global DNA hypermethylation was hypermethylated CpG loci. ● Moreover, the hypermethylation of *Bcl-2* and *CREB3L1* gene promoters.	Zou et al., 2016
	Human HaCaT cells	2.5–10 µg/mL SiO_2-NPs for 24 h	● It was shown that the global DNA hypomethylation decreased significantly. There was a significant reduction of DNMT3A, DNMT1, and MBD2 levels (methyl GpG binding protein 2).	Gong et al., 2010
	Mouse Bhas 42 cells	15 or 25 µg/cm^2 of the crystalline silica particles Min-U-Sil® 5 for 48 h	● Results indicated a substantial reduction in global DNA methylation (~80%). ● Both DNMT3A and DNMA3B significantly increased response to SiO_2-NPs exposure.	Seidel et al., 2017
	Human HaCaT cells	10 µg/mL and 100 µg/mL of SiO_2-NPs for 24 h	● Decreased methylation of Alu repetitive fundamentals. Results clarified promoter hypermethylation and diminished transcript of PARP1 protein.	Sooklert et al., 2019; Gong et al., 2012
TiNPs	Human MRC5 lung fibroblasts	0.5 or 4 µg/mL for 24 and 48 h	● Global DNA hypomethylation. ● Reduced total DNA methyltransferase activity.	Patil et al., 2016
	Human lung epithelial cells (A549)	TiO_2.NPs 40 µg/cm^2 for 48 and 72 h	● Hypomethylation in DNA. ● Demethylation of LINE1 repetitive essentials.	Stoccoro et al., 2017
	Human small airway epithelial cells	0.5 and 30 µg/mL for 24 h	● Demethylation of SINE B1 repetitive.	Lu et al., 2016 a, b
	Human lung (NL20), skin (A-431), hepatic (HepG2), and colon (CaCo-2) cells	100 µg/mL for 24 and 72 h	● DNA hypomethylation in some cell lines, including HepG2, Caco-2, and A-431 cells. ● Up-regulation of some methylation genes such *BNIP3* , *CDKN1A, DNAJC15, GADD45A, SCARA3, GDF15, INSIG1, TP53*. ● Additionally, altered transcript of *DNMT3B*, *MBD2*, *DNMT1, DNMT3A,* and *UHRF* genes.	Pogribna et al., 2020

Table 1 – contd.

1	2	3	4	5
Au-NPs	Human kidney embryonic (HEK293 cells)	100 µg/mL of Au-NPs for 72 h	● Hypomethylation in global DNA.	Sooklert et al., 2019
Au-NPs	Human skin fibroblasts	62.5 µg/mL for 24 and 48 h	● Global DNA hypomethylation.	Patil et al., 2019
Au-NPs	Human breast cancer (SK-BR-3) cells	3 µg/mL for 24, 48, and 72 h	● No effect on global DNA methylation.	Smolkova et al., 2016
Au-NPs	Human hepatic HepG2	10 µg/mL for 24 h	● No effect on global DNA methylation.	Brzóska et al., 2019
Au-NPs	Human fetal fibroblasts (MRC5)	1 nM of AuNPs for 48 and 72 h	● No effect on global DNA methylation.	Ng et al., 2011
Ag-NPs	HT22 hippocampal mouse	1–20 µg/mL of Ag-NPs for 48 h	● Increase in DNA methyltransferases DNMT1, DNMT3A, and DNMT3B.	Mytych et al., 2017
Ag-NPs	Human BEAS-2B	1 µg/mL Ag-NPs for 6 weeks	● Marginal effects on DNA methylation: one differentially methylated gene promoter corresponding to a gene (ENSG00000250358), six differentially methylated CpG sites and five differentially methylated tiling regions.	Gliga et al., 2018
Ag-NPs	Human lung (A549)	10–200 µg/mL Ag-NPs for 48 and 72 h	● Global DNA hypermethylation.	Blanco et al., 2017
Ag-NPs Au-NPs Magnetite (Fe_3O_4) SPIONs	Human hepatic cell (HepG2)	10 µg/mL Ag-NPs, 10 µg/mL Au-NPs, 5 µg/mL SPIONs for 24 h	● No changes in promoter methylation of genes related to inflammation and apoptosis for any NPs studied.	Brzóska et al., 2019
ZnNPs	Human MRC5 lung fibroblasts	4 or 8 µg/mL for 24 and 48 h	● Global DNA hypomethylation decrease in total DNA methyltransferase activity.	Patil et al., 2016
ZnNPs	Human embryonic kidney (HEK293)	25 or 50 µg/mL for 48 h	● Global DNA (5-mC) hypomethylation. Increase in DNA hydroxymethylation (5-hmC) associated with increased expression of *TET1* and *TET2* genes.	Choudhury et al., 2017

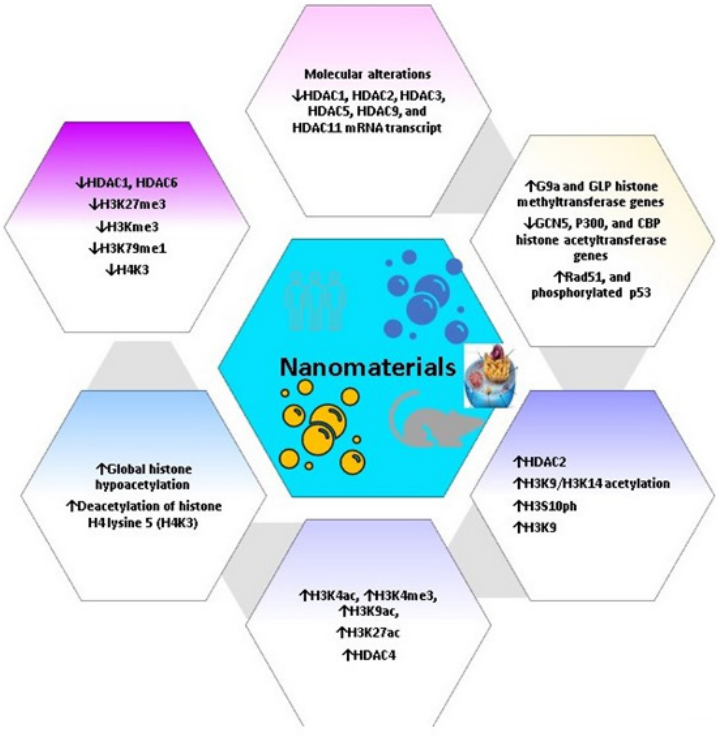

Figure 3. Potential impacts of nanomaterial on the histone modifications, some specific gene expression and histone-modifying enzymes collected from *in vitro* and *in vivo* studies

Moreover, in other studies on MWCNTs, hypermethylation in 2398 and 501 genes was observed in the individual *CpG* sites and the promoter and genomic regions of the body, respectively, including the *GSTP1*, *SHROOM2, SKI*, and *NF1*gene as evidenced by multiple authors (Öner et al., 2017; Ghosh et al., 2018).

After exposure to SWCNTs, at minimum, one site of CpG has methylated in *MYO1C*, *DNMT1*, *MAP3K10* and *HDAC4*; subsequently, exposure to MWCNTs, and in *PIK3R2* and *NPAT/ATM* after exposure to SWCNTs in addition to MWCNTs. On the opposite side of gene-specific alterations through DNA methylation, no variations in the global cytosine DNA methylation level were detected in MWCNTs and SWCNTs-subjected cells (Ghosh et al., 2018; Öner et al., 2018). Nevertheless, Emerce et al. (2019) revealed that in 16HBE14 cells subjected to MWCNTs, significant damage to global DNA methylation was detected.

Silica nanoparticles (SNPs)

Like other nanomaterials, exposing human HaCaT cells to silica nanoparticles (SNPs) at levels 2.5–10 μg/mL induced reduction in the DNMT3A and DNMT1 proteins expression, in terms of global DNA hypomethylation (Gong et al., 2010). The changes of DNMT1 might be associated with developing various syndromes in human body, therefore demonstrating a promising therapeutic mark. According to previous investigations (Seidel et al., 2017; Sooklert et al., 2019), similar effects of SNPs-induced DNA hypomethylating were detected in other human cells, indicating the negative effects of SNPs on DNA methylation.

In a previous study conducted on mice, it was observed that the global DNA methylation was decreased significantly (80%) associated with augmented DNMT3B and DNMT3A proteins levels subjected to SNPs (15 or 25 μg/cm^2) for two days (Seidel et al., 2017). Moreover, treating human HaCaT cells with SNPs (10 μg/mL) induced hypermethylation and reduced transcript of PARP1 protein (Gong et al., 2012). Zou et al. (2016) reported that the SNPs sub-cytotoxic treatment of BEAS-2B cells (human bronchial epithelial, five μg/mL) presented significant DNA hypermethylation alterations, which was manifest by a principal quantity (1973) of hypermethylated CpG loci over 223 hypomethylated CpG loci. The same authors revealed that the *BCL-2* and *CREB3L1* gene promoters were hypermethylated with significantly reduced BEAS-2B cells (human bronchial epithelial) transcriptomic alteration.

Titanium dioxide nanoparticles (TiNPs)

Titanium dioxide nanoparticles (TiNPs) are commonly used in various industrial products and water purification. Many studies have clarified that global DNA methylation is considered one of the main epigenetic modifications induced by TiNPs exposure (Patil et al., 2016; Stoccoro et al., 2017; Pogribna et al., 2020). For instance, Stoccoro et al. (2017) explored the methylation of cellular DNA in lung epithelium (A549) after human exposure to TiNPs. They found a substantial lack of global DNA methylation, as proved by noteworthy demethylation of LINE1 repetitive essentials, through the soundest upshot shown by TiNPs. In another study, the application of 0.5 or 4 μg/mL TiNPs for one or two days to the lung fibroblast cells (MRC5) induced a reduction in the global DNA methylation, as supported by Patil et al. (2019). Generally, it is accepted that a decrease in DNA methyltransferase activity escorts these changes in DNA methylation. Recently, Pogribna et al. (2020) clarified that non-toxic dosages of TiNPs were observed in human colon (Caco-2), liver (HepG2), lung (NL20), and skin (A-431) cells for 1–3 days. They concluded that TiNPs considerably decreased the global DNA methylation as previously mentioned cells. Conversely, the same authors illustrated that the genetic methylation of *GADD45A, DNAJC15, INSIG1, CDKN1A, SCARA3, GDF15, TP53,* and *BNIP3* was augmented in human cells (Pogribna et al., 2020). In addition, maintaining DNA methylation genes (*MBD2, DNMT3B, UHRF DNMT1,* and *DNMT3A*) were upregulated in human cell lines as a response to exposure to TiNPs (Pogribna et al., 2020). Based on the molecular and cellular influences, such as the genotoxic effects of the exposure of TiNPs have been widely explored. However, their epigenetic properties still lack decisive information.

Zinc oxide nanoparticles

Parallel to TiNPs, the zinc oxide nanoparticles (ZnNPs) significantly influenced global DNA methylation and induced DNA damage when exposed for long periods. After ZnNPs treatment (either 4 or 8 μg/mL) for 24 and 48 h, this DNA damage was markedly decreased in lung fibroblast cells (MRC5) (Patil et al., 2016). Similarly, ZnNPs caused DNA demethylation through a noticeable reduction in locus-specific-DNA hypomethylation levels. In addition, 5-meC in DNA escorted by the downregulation of *DNMT3B* and *DNMT1* genes in HEK293 cells (a type of human embryonic kidney) treated with ZnNPs (25 or 50 μg/mL) for 48 h was described by Choudhury et al. (2017). Remarkably, ZnNPs (50 μg/mL) induced a considerable upsurge in the 5-hmeC levels in DNA, which was accompanied by augmented transcripts of certain genes, including TET1 and TET2. These changes in the methylation of DNA were associated with a decrease in DNA methyltransferase action.

Gold and silver nanoparticles

Plasmonic metal-originated nanoparticles have a high possibility for biological and chemical sensor applications because of their sensitive, ethereal reactivity to the environment surrounding the surface of nanoparticles and ease of light signal monitoring owing to their strong absorption or scattering (Lee and El-Sayed, 2006). Several studies have inspected the impacts of gold (AuNPs) and silver (AgNPs) nanoparticles on cytosine DNA methylation. As reported previously, human em-

bryonic kidney (HEK293) cells exposed to high levels of AuNPs (100 µg/mL) for three days exhibited a considerable lowering in global DNA methylation (Sooklert et al., 2019). On the contrary, AuNPs had no considerable effects on DNA demethylating activity in numerous studied cell lines, for example, MRC5 fetal fibroblasts (Ng et al., 2011), human breast cancer cells (SK-BR-3; Smolkova et al., 2016), as well as HepG2 hepatic cancer cells (Brzóska et al., 2019). These disturbances of the impacts of AgNPs on global DNA methylation might be associated with the type of cell line, level of NMs, experimental conditions, duration of exposure, and synthesis of nanomaterial (such as chemical or biogenic methods). Gold nanoparticles (AuNPs) have been applied technologically in different biomedical sciences. For this concept, exploring the potential effects of genomics alteration is interesting. In another study on mice, Mytych et al. (2017) clarified that hippocampal neuronal (HT22) cells exposed to AgNPs (5 µg/mL) triggered noticeable DNA hypermethylation of genomic cytosine. Moreover, the same work found a significant up-regulation of DNA methylation-related genes such as DNMT3A, DNMT1 and DNMT3B (Mytych et al., 2017). Additionally, high levels of AgNPs (200 µg/mL) induced a significant augmentation in the global cytosine DNA methylation of A549 human lung adenocarcinoma cells. In addition, Gliga et al. (2018) established a slight impact of AgNPs (1 µg/mL) for six weeks on the methylation of DNA in human BEAS-2B cells. Many previous investigations have revealed that Ag-NPs (up to 100 µg/mL) did not substantially affect the global cytosine DNA methylation in human cell cancers (Blanco et al., 2017; Brzóska et al., 2019). It is clear that AgNPs have disturbing results on DNA methylation, which might be the different AgNPs levels, duration of exposure, type of cell lines and additional topics are required.

Effects on DNA methylation (*in vivo* model)

There is a lack of information about nanomaterial's potential effects on DNA methylation in *in vivo* experiments (Table 2 and Figure 3).

In mice, significant hypomethylation of global DNA and considerable reduction of *Tnf-a* and *Ifn*-ɣ genes were noticed in leukocytes and lung tissue as a response to the exposure to a 50 µg of single oropharyngeal MWCNTs instillation for one week (Brown et al., 2016). Both genes *Tnf-a* and *Ifn*-ɣ are associated with inflammation. In mice exposed to a single intra-tracheal instillation of AgNPs for 24 h (Lu et al., 2016 a, b), an increase by 25% and 50% for global 5-meC and 5-hmeC, respectively. Moreover, the activation of a 5-hmeC promotion in the treated mice lung tissue was associated with the increased expression of both *SINEB1* and *LINE1* genes. Recently, carbon NPs (10 or 30 µg/mL with 50 nm) produced a noticeable improvement in the methylation of cytosine DNA, nevertheless significant methylation of gene promoters (*Teleostean IL11b, lepb*, and *cd248b)* in zebrafish (Zhou et al., 2019).

Parallel with previous studies, Hu et al. (2019) lately reported that changes in DNA methylation were observed when zebrafish were exposed to 2, 10, and 50 µg /L of NPs for seven days, which caused a considerable increase in global DNA methylation.

The last authors (Hu et al., 2019) theorized that 5-hmeC rise was related to reduced Tet1 gene transcription, which codes a chief *TET1* (methylcytosine-deoxygenase). This pattern could consecutively transform 5-meC into 5-hmeC, consequently converting into 5mC and 5fC (5-formyl cytosine) throughout the active demethylation of DNA (Chouke et al., 2022). Still, we need further explorations for support and evidence of the potential effects of carbon dots on DNA methylation in *in-vitro* models for being safer and more peaceful when using those materials.

Moreover, Tabish et al. (2017) investigated the impacts of AuNPs on lung gene-specific methylation in mice. Authors observed that a single instillation in the trachea (AuNPs 60 nm for 48 h after instillation) induced hypomethylation of *Gpx* and hypermethylation of *Cdk*, *Gsr*, and *Atm* in mice lung tissues. Moreover, the previous study found that up-regulation of 17 genes was reported after the administration of AgNPs in mice. Xenobiotic experiences frequently trigger these genes. Exposure of mice to copper nanoparticles (2.5 mg/kg BW) for one day reduced considerable hypermethylation of DNA (Lu et al., 2016 a, b). Moreover, the indicators of DNA methylation including DNMT*3b*, *Dnmt3a*, *Tet1*, and *Dnmt1* were significantly reduced in lung tissues. However, only one study had the opposite results. In contrast, Rossner et al. (2020) observed non-significant variation in global DNA methylation, despite the noticeable alterations of transcription.

Human studies

In 2004, the Nanotechnology Research Center (NTRC) was established by the National Institute for Occupational Safety and Health (NIOSH) to address health concerns and occupational safety linked with engineered nanomaterials (Fischman et al., 2011). Once in the environment, nanomaterials may interrelate with metabolic systems and cellular ingredients in various human tissues. The study of Liou et al. (2017) investigated the degree of DNA methylation in white blood cells from Taiwan workers (n=31 *vs* n=43 for control one) who had worked in nanomaterial manufacturing and/or handling factories. Considerable reduction in global DNA methylation was found in people who worked in these industrial regions (Liou et al., 2017).

Rossnerova et al. (2020) found significant shifts in CpG methylation, with 341 CpG sites turning hypomethylated and 364 getting hypermethylated in people exposed to NMs. Moreover, the levels of DNA oxidative markers such as 8-OHdG (8-hydroxy-2′-deoxyguanosine) in white blood cells (WBCs) and urine fluid exposed to NMs were altered. Moreover, Ghosh et al. (2022) discovered a substantial alteration in methylation at in-

dividual CpG sites situated in the promoter districts of the HDAC4, SKI, ATM, and DNMT1 genes in people exposed to MWCNTs. On the other hand, Rossnerova et al. (2020) discovered that short-time exposure had no impact on DNA methylation in the WBCs of 20 workers.

Effects on histone modifications

Another epigenetic change as a response to nanomaterial exposure is histone modifications. It was previously reported that NMs induced significant results on global DNA methylation in animals and humans. Histone modifications, which include phosphorylation, methylation, and acetylation of the N-terminal tails of histone proteins, are further main machinery of the epigenetic regulatory system. Generally, histone modifications are catalyzed by precise enzymes in various involving amino acids, including arginine, serine, lysine, threonine, tyrosine, etc. In addition, histone methylation has either transcriptionally oppressive or permissive features, contingent on the position of targeted amino acid residues in the histone tail and/or the additional quantity of methyl groups (Alaskhar Alhamwe et al., 2018). For histone acetylation regularly leads to greater post-transcription (Torres and Fudjimori, 2015). Histone has various aspects, such as histone phosphorylases, methyltransferases, and acetyltransferases. These features introduce specific chemical modifications, whereas histone "erasers", such as histone phosphatases, demethylases, and deacetylases, are responsible for erasing chemical alterations. Studies have found that aberrant histone modification outlines are closely connected with various syndromes based on *in vitro* or *in vitro* trials.

Table 2. Effects of different nanomaterials on DNA methylation (*in vivo* models)

Nanomaterials	Cells	Doses	The main findings	Reference
CNTs (MWCNTs)	Workers (n=24)	Occupationally exposed to the MWCNTs for seven days	● No difference in global DNA methylation (5-mC) or DNA hydroxymethylation (5-hmC). Changes at individual CpG sites in the promoter region of DNMT1, ATM, SKI, HDAC4.	Ghosh et al., 2017
SiO_2-NPs	Worker (n=31)	Handling factories in Taiwan exposed to SiO_2-NPs	● Global DNA hypomethylation.	Liou et al., 2017
SiO_2-NPs	Workers (n=20, white blood cells)	Long-term occupational exposure (mean time 14.5 years) to nanocomposite materials containing up to 20% SiO_2-NPs	● Long-term exposure caused changes in CpG methylation: 341 CpG sites hypomethylated, 364 CpG sites hypomethylated. Short-term exposure did not affect DNA methylation patterns.	Rossnerova et al., 2020
CNTs: MWCNTs	C57BL*J*6 mice	25 µl of MWCNTs	● Genes hypomethylation in lung tissue and blood. Decrease in EFN-γ methylation. ● TNF-α promotor hypomethylation. ● Increase of methylation in *Thy-1* promotor.	Patil et al., 2016
Carbon nanoparticles (CNPs)	Adult zebrafish (*Danio rerio*)	CNPs (0, 10 and 30 µg/mL) suspensions for 60 days	● Upregulation of dnmt3b and Tet2 in heart tissue Dose-dependent decreases in the mRNA expression of dnmt1, dnmt3a, and Tet1. ● Promoter demethylation of lebp, cd248b, and il11 Increase in transcriptions for lebp and cd248b in the high-dose group.	Zhou et al., 2019
Nano-graphene quantum nanodots (M-GQDs)	Zebrafish	2, 10, and 50 mg/L nano-graphene quantum dots for seven days	● Global DNA hypermethylation (tissue-specific and dose-dependent).	Hu et al., 2019
Laser printer-emitted nanoparticles	BALB/c mice	Single intra-tracheal instillation of 2.5 mg/kg body weight of laser printer-emitted engineered nanoparticles for 24 h.	● Increase in the global level of 5-meC by 25% and 5-hmeC by 50%.	Lu et al., 2016 a, b
Au-NPs	BALB/c mice	5-, 60- and 250-nm Au-NPs at 2.5(intratracheal administration) and 0.25 mg/mL for 48 h	● No effect on global DNA methylation and DNA hydroxymethylation. Promotor hypermethylation in *Atm*, *Cdk*, and *Gsr* genes in mouse lung tissue. Promotor hypomethylation in *Gpx* gene in mouse lung tissue.	Tabish et al., 2017
Copper (II) oxide NPs (CuO-NPs)	BALB/c mice (lung tissue)	2.5 mg/kg of copper (II) oxide (CuO)-NPs	● Global DNA hypermethylation. Reduced expression of DNA methyltransferases, *Dnmt1*, *Dnmt3a*, and *DNMT3b*, and *Tet1*.	Lu et al., 2016 a, b
CuO-NPs	Female ICR mice	8×10^5 CuO-NPs in a whole-body inhalation chamber for two days to three months	● No changes in global DNA methylation.	Rossner et al., 2020

Histone H2AX phosphorylation

The phosphorylation of histone H2AX at serine-139 (ɣ-H2AX) has been presented to be associated with mitotic chromosome condensation. For the impacts of NMs on ɣ-H2AX, multiple reports indicated that NMs enhanced the synthesis of γ-H2AX, which might attributed to the augmented intracellular oxidation, which could encourage oxidative DNA lesion (Zhao et al., 2016; Liu et al., 2017; Kopp et al., 2018; Könen-Adıgüzel et al., 2018).

One of the early DNA damage reactions, ɣ-H2AX is widely known to be produced in response to many kinds of DNA damage (Kopp et al., 2018). Research shows that exposing human cancer cells to 1.0 g/mL Ag-NPs for 4 hours caused the development of ɣ-H2AX in human breast adenocarcinoma (MCF-7) cells and lung adenocarcinoma (A549) cells, while no considerable effects were detected in human skin keratinocytes (HaCaT) (Zhao et al., 2016). Moreover, Blanco et al. (2017) revealed that A549 cells treated with Ag-NPs (10–200 g/mL) for 2–3 days induced ɣ-H2AX. Similar effects of Ag-NPs, TiO_2-NPs showed significant induction of ɣ-H2AX in several human cell lines, including dermal, skin fibroblasts, and intestinal Caco-2 cells (Prasad et al., 2013; Setyawati et al., 2013; Tarantini et al., 2015).

Examples of the ɣ-H2AX modifications brought on by exposure to well-known nanomaterials are shown in Table 2 in both *in vitro* and *in vivo* sceneries.

As indicated by many investigations (Kung et al., 2015; Könen-Adıgüzel et al., 2018; Liu et al., 2018; Surapaneni et al., 2018), exposing various cells of humans has a considerable effect on increasing ɣ-H2AX levels as influenced by Au-NPs, zinc oxide (ZnNPs), arsenic trioxide (As_2O_3-NPs), cerium dioxide (CeO_2-NPs), and copper oxide (CuO)-NPs. The results based on the literature regarding the effects of NMs on ɣ-H2AX are still conflicting and need further clarification. Moreover, the association between H2AX and oxidative-related markers is unexplored.

In addition to ɣ-H2AX induction, NMs and NPs produce other histone alterations (Table 2).

Both histones H3 and H4, as well as the HDAC2 protein acetylation, were significantly augmented in mice exposed to SNPs (15 or 25 μg/cm^2), while the levels of HDAC1 and HDAC6 protein were reduced (Seidel et al., 2017). HDAC2 is an important regulator of Arg2 transcript, thus regulating different biological actions of the cell cycle, apoptosis, differentiation, and cancers. Moreover, H3K27ac, H3K9ac, H3K4ac, and H4Kme3 singling were augmented at the over-expressed *c-myc* gene promoter domain (Seidel et al., 2017). Furthermore, human A549 cells treated with 50 μg/mL SNPs for 3–12 hours resulted in HDAC, SIRT6 mRNA destabilization, and inferior SIRT6 protein and transcript (Zhang et al., 2018). In another experiment, Lv et al. (2015) used human adipose-derived stem cells (hASCs) and treated them with TiO_2 nanotubes (70 nm) to induce osteogenic differentiation. Consequently, the osteogenic differentiation of hASCs, as affected by exposure to TiO_2 nanotubes, was related to augmented osteogenic genes and *RUNX2* histone H_3K_4 methylation and further histone demethylase *RBP2* was repressed by TiO_2 treatment. Studies have shown the potential effects of AuNPs on histone modifications in many *in vivo* models (Shyamasundar et al., 2015). For instance, studies have revealed that the NMs such as AuNPs or arsenic trioxide NPs (0.2–0.8 μM) resulted in a significant reduction in histone H3 lysine 27 trimethylation (Shyamasundar et al., 2015), and histone H4K16 in HEK293 (human early-stage kidney) or HeLa cells (Liu et al., 2015). Conversely, exposure at the level of 100–500 μg/mL of AuNPs positively charged AuNPs caused increased acetylation of H3K9/H3K14 and phosphorylation of histone H3Ser10 (Surapaneni et al., 2018).

Additionally, several studies have confirmed that the different levels of AgNPs (0.3, 1, 10, 200 μg/mL) affected human HaCaT, A549, and MCF-7 cells (Johansen and Johansen, 2006; Zhao et al., 2016; Blanco et al., 2017) through increased histone H3 serine 10 (H3Ser10ph) phosphorylation, deacetylation histone H3 deacetylation, DNA lesion, a mitotic chromatin condensation-associated modification (Zhao et al., 2019). Significant reductions in specific DNA methylation genes such as HDAC5, HDAC3, HDAC2, HDAC1, and HDAC11 were noticed in A549 cells treated with CuNPs for 36 h (Kalaiarasi et al., 2018). The same results were evidenced by Qian et al. (2015), who clarified that a noticeable reduction in levels of global and β-globin gene-specific H3K79me1 (histone H3 lysine 79 monomethylation) and H_3K_4me3 (histone H3 lysine 4 trimethylation) were detected in erythroleukemia cells of mouse treated with AgNPs (8 μg/mL) for 72 h.

ZnNPs are another nanoparticle that has been widely used in several industrial fields. For this reason, it is interesting to explore the potential effects of this NM on histone modification in *in vivo* models. Moreover, clarification implemented by Gao et al. (2016) has found the manifest H4K5 (histone H4 lysine 5) deacetylation and augmented demethylation of H_3K_9 (histone H3 lysine 9) in HaCaT cells treated with ZnNPs (20 or 50 μg/mL) for 24 h. This modification might be associated with the down-regulation of CBP, P300, and GCN5, histone acetyltransferase genes and increased methyltransferase genes such as G9a and GLP (Gao et al., 2016). Recently, human bladder cancer (T24 cells) exposed to ZnNP (10 μg/mL) had diminished the histone H3K27 trimethylation levels and at the *RUNX3* gene promoter (Zhang et al., 2020). They suggested that these fluctuations of histone modifications might be associated with the down-regulation of histone H3K27 methyltransferase EZH2. Data is scarce recounting the toxicity of NMs used in animal and human studies.

Nanomaterials-induced DNA methylation and histone modification

Changes in epigenetic machineries are complicated by the etiology and the development of several syndro-

mes comprising cancer, metabolic, neurological complaints and cardiovascular syndromes (Alaskhar Alhamwe et al., 2018; Musolino et al., 2022). However, in the normal physiological state of a cell, epigenetic actions are developed and naturally occur. In other abnormal cases, such as exposing cells to NMs, could alter the coding RNA and non-coding RNAs as well as post-transcriptional regulatory genes. Studies have clarified the faultless maintenance of cytosine DNA methylation and histone modifications as a response to NMs in various mammalian cells, comprising the status of intracellular metabolism, the suitable function of chromatin-modifying proteins, particularly chromatin integrity, and one-carbon metabolism (Fischman et al., 2011; Musolino et al., 2022). Based on many kinds of literature (Figure 4), it was concluded that the main prevalent reflection specific to the majority of trials is the initiation of apoptosis, inflammation and increase in the synthesis of oxidative stress (Wan et al., 2012; Brown et al., 2016; Hanot-Roy et al., 2016; Dusinska et al., 2017).

The previous events, including oxidative stress, inflammations, and apoptosis, might affect the chromatin intactness and lead to DNA methylation and histone modifications changes (Figure 4), as reported by several investigations (Dusinska et al., 2017; Long et al., 2019; Jiang et al., 2020).

Trials (Valinluck et al., 2004; Sahafnejad et al., 2023; Szczepanek et al., 2023) have shown several DNA lesions including 5-hmeC, 8-OHdG and constrained methylation capability of DNA methyltransferases, causing global DNA hypomethylation due to exposure to NMs.

Furthermore, the outcomes of various independent reports have confirmed that NMs and NPs, e.g., TiONPs, ZnNPs, MWCNTs, etc., can diminish the anti-oxidative defense in the cellular system as well as trigger the inflammation/oxidative signaling (Patil et al., 2016; Long et al., 2019). These alterations could start a bundle of intracellular reactions ending up with the demethylation of DNA and histone alterations (Wu and Zhang, 2017; Öner et al., 2018; Sima et al., 2020). Moreover, based on Chouke et al. (2022), the inflammation in the cellular system triggered the DNA lesion and finally modified the DNA methylation or caused hypomethylation. Since previously unmethylated CpG sites can imitate 5-meC and be directly methylated, the prevalence of inflammation-mediated halogenated cytosine damage products in DNA, such as 5-chlorocytosine and 5-bromocytosine, encourages aberrant hypermethylation (Valinluck and Sowers, 2007). Furthermore, it has been shown that oxidative DNA damage can cause both DNA demethylation and the creation of new methylation sites at unmethylated CpG sites (Jiang et al., 2020). However, the machineries of action by which the NMs could trigger epigenetic toxicity are not yet entirely understood and need further exploration.

Safety of nanomaterials and the epigenetic roles

The uses of nanoparticles are increasingly relevant in various fields, including cosmetic, industrial, construction, electronic, and environmental arenas. Thus, assessing the toxicological danger accompanying NMs should be reflected as an important part of their design and manufacture to ensure our environment's safety, trades and workers in the fields. Studies have revealed that NMs illustrate epigenetic changes, which may be applied to distinguish toxicity effects brought on by designed nanomaterials and, more crucially, to anticipate in preclinical evaluations (Francés et al., 2023; Lebre et al., 2022). However, numerous *in vitro* and *in vivo* experiments have been achieved focusing on the toxicity of NMs on mammalian cells (Lv et al., 2015; Zou et al., 2016; Seidel et al., 2017), the research on nanotoxicology is still in its beginning. Moreover, there are gaps in comprehending the nanoparticle's effects and its relation with human and environmental risks.

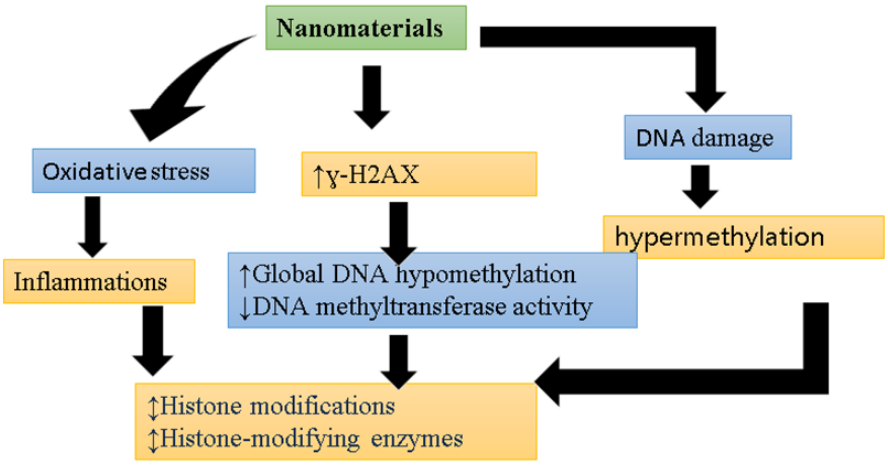

Figure 4. Nanomaterials (high doses) induced oxidative stress and inflammation biomarkers in the cellular system. This leads to DNA damages, and triggers hypermethylation of DNA and alters the global DNA methyltransferase activities. Moreover, nanomaterials increased γ-H2AX and induced changes in histone modification through disturbances of histone-modifying enzymes

This can be demonstrated by the damage of global DNA methylation found in rats, humans and other cell lines after silica nanoparticles treatment *in vitro* (Seidel et al., 2017; Sooklert et al., 2019; Liou et al., 2017) which presented a notable decrease in global cytosine DNA methylation in white blood cells from workers dealing with SiNPs. Inclusively, the previous data provided the first set of the argument of epigenetic modifications triggered by exposure to nanomaterials. However, more longitudinal population investigations are needed to provide more comprehensive data.

Epigenetic manipulators

Based on the findings mentioned above, it is clear that several biological and pathological situations complicate nanomaterials. For instance, nanomaterials induced multi-epigenetics changes, including DNA damage, histone modification and DNA methylation, chromatin structure and DNA accessibility alteration, whereby regulating gene expression patterns. Studies have evidenced that many dietary regimens have demonstrated a remarkable effect in epigenetic modulation for alleviating the potential effects of nanomaterials. Likewise, the modulating effect of dietary factors alongside DNA methylation and epigenetics changes could depend on serving as a cofactor in metabolic pathways (Romanek, 2013; Saeed et al., 2017 a, b; Samiec and Skrzyszowska, 2018). Distinct genetic modifications and epigenetic situations of some specific genes are reversible and can be changed by extrinsic and intrinsic features. In nutrigenomics and nutrigenetics, some nutritional compounds presented epigenetic roles comprising nutrients precisely targeting histone modifications and DNA methylation (Skrzyszowska and Samiec, 2020; Semik-Gurgul et al., 2022).

Phytochemicals

The augmentation of H3K9 and HDACS inhibition at the proximal region of p27 and p21 promoters indicated a notable up-regulation of p21 and p27 transcripts by tocotrienols (Huang et al., 2017). Moreover, in another study, Jou et al. (2015) found that the administration of γ-bisabolene decreased the DNA phosphorylation marker (HDAC2) while boosting the transcript of p53, ERK1/2 and PP1 (protein phosphatases 1). Consequently, γ-bisabolene, as a powerful phytochemical agent, is a possible epigenetic modifier that can be assessed further for developing epigenetics enhancers (Abd El-Hack et al., 2018; Gado et al., 2019).

As reported above, NMs lessen the action of histone methyl transferases accompanied by H3K27me3 reduction. Luteolin has dual inhibitory activity against histone methyltransferases and DNA methyltransferases (Kanwal et al., 2016). Additionally, luteolin has a high affinity to inhibit HDAC8 (Mira and Shimizu, 2015). This indicates that luteolin has the potential to be discovered further for expanding as a therapeutic mediator alongside various ailments (Zuo et al., 2018). Several other phytochemical compounds are evidenced by their significant role in epigenetic modifiers, such as epigallocatechin, garcinol, garlic, quercetin, and apigenin (Alagawany et al., 2014, 2016; Saeed et al., 2017 a, b, 2018; Abdel-Moneim et al., 2020). Those previous compounds could present as DNA hypermethylating agents (Abd El-Hack et al., 2016, 2018, 2020, 2021; Khafaga et al., 2019; Gupta et al., 2020; Mehana et al., 2022).

Micronutrients

Generally, micronutrients such as vitamins and minerals are an indispensable portion of the diets of animals or humans, which show an imperative function in metabolism and absorption and might regulate certain vital events by acting as a cofactor. Based on the screening studies, the best micronutrient is folic acid, which is used to modify the methylenetetrahydrofolate gene (Pascoal et al., 2022).

DNA methylation through DNMT catalyzes the methyl group transfer from S-adenosyl methyltransferase to specific regions in DNA segments (Kanwal et al., 2016). Vitamins such as B_6, B_{12}, choline, folic acid, and methionine highlight the role of vitamins in the epigenetic machinery (Fenech, 2008). Regarding minerals, selenium is documented as an epigenetic modulator in animals (Pascoal et al., 2022). The previous study reported that dietary selenium supplementation showed a significant role against obesity-induced deregulation of epigenetic variables (Dnmt3a) in spermatogenesis in a rat model. Moreover, some evidence suggested that selenium supplementation has an epigenetic modulator owing to its powerful antioxidant action, DNA-repairing mechanism, and pro-apoptotic capability (Liang et al., 2022).

Moreover, selenium displays DNA demethylation and recurrence of GSTP1 genes in some cell lines. Selenium also augments the acetylation of H3K9 declines and histone deacetylase activity (Ghanghas et al., 2022). Correspondingly, zinc and magnesium are chief microminerals as cofactors in DNA repair genes (OGGI), DNA polymerases responsible for oxidized guanine removal (Fenech, 2008). The potentiality of using the other essential microelements as epigenetic regulators are unexplored and needs further explorations in the upcoming years.

Conclusions and future remarks

Based on the collected information from several studies regarding the use of designed nanomaterials which were widely described, their stability was tested before use *in vitro* or *in vivo*. Moreover, clarifying the influence of NMs on the epigenome will allow for outlining latent toxicity and consequently describing more precisely the toxicity of these NMs. Nanomaterials demonstrated significant adverse effects on various molecular and cellular alterations. The epigenetic modifications, including histone modification and DNA methylation, chromatin structure and DNA accessibility alteration, regulate gene expression as a response to NMs. This is connected to the fact that numerous investigations have utilized various human cell types as cell lines or animal models, various

exposure times, occasionally highly toxic doses of nanomaterials, and various procedures in the investigation of epigenetic modifications, ranging from straightforward methods of global DNA methylation examination to the genome-wide association. Therefore, it is unclear whether NMs and NPs exposure directly impacted epigenome or if the alterations associated with exposure were brought on by cellular toxicity. Accordingly, epigenetic effects triggered by NMs should always be considered during nano-toxicity investigations and during the development and assessment of novel epigenetic drugs. Some epigenetic modulators helped restore the epigenetic changes by NMs, such as phytochemical and microelements. Future well-controlled and well-designed studies are required to understand better the machinery and processes connected with epigenetic modifications by nanomaterials.

Conflicts of interest

All authors declare that they have no conflicts of interest that could inappropriately influence this manuscript.

Author contribution

All authors contributed equally to writing this review article. All authors read and approved the final version of this manuscript.

Data availability statement

No data are available.

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References

Abd El-Hack M.E., Alagawany M., Farag M.R., Tiwari R., Karthik K., Dhama K. (2016). Nutritional, healthical and therapeutic efficacy of black cumin (*Nigella sativa*) in animals, poultry and humans. Int. J. Pharmacol, 12: 232–248.

Abd El-Hack M.E., Alagawany M., Arif M., Emam M., Saeed M., Arain M.A., Khan R.U. (2018). The uses of microbial phytase as a feed additive in poultry nutrition – a review. Annals Anim. Sci., 18: 639–658.

Abd El-Hack M.E., Shafi M.E., Alghamdi W.Y., Abdelnour S.A., Shehata A.M., Ragni M. (2020). Black soldier fly (*Hermetia illucens*) meal as a promising feed ingredient for poultry: A comprehensive review. Agriculture, 10: 339.

Abd El-Hack M.E., El-Saadony M.T., Shehata A.M., Arif M., Paswan V.K., Elbestawy A.R. (2021). Approaches to prevent and control *Campylobacter* spp. colonization in broiler chickens: a review. Environ. Sci. Poll. Res., 28: 4989–5004.

Abdel-Moneim A.M.E., Shehata A.M., Alzahrani S.O., Shafi M.E., Mesalam N.M., Taha A.E., Abd El-Hack M.E. (2020). The role of polyphenols in poultry nutrition. J. Anim. Physiol. Anim. Nutr., 104: 1851–1866.

Alagawany M., Abd El-Hack M.E., Laudadio V., Tufarelli V. (2014). Effect of low-protein diets with crystalline amino acid supplementation on egg production, blood parameters and nitrogen balance in laying Japanese quails. Avian Biol. Res., 7: 235–243.

Alagawany M., Abd El-Hack M.E., El-Kholy M.S. (2016). Productive performance, egg quality, blood constituents, immune functions, and antioxidant parameters in laying hens fed diets with different levels of *Yucca schidigera* extract. Environ. Sci. Poll. Res., 23: 6774–6782.

Alaskhar Alhamwe B., Khalaila R., Wolf J., von Bülow V., Harb H., Alhamdan F., Potaczek D. P. (2018). Histone modifications and their role in epigenetics of atopy and allergic diseases. Allergy Asthma Clin. Immunol., 14: 1–16.

Ameh T., Sayes S.M. (2019). The potential exposure and hazards of copper nanoparticles: a review. Environ. Toxicol. Pharmacol., 71: 103220.

Blanco J., Lafuente D., Gómez M., García T., Domingo J.L., Sánchez, D.J. (2017). Polyvinyl pyrrolidone-coated silver nanoparticles in a human lung cancer cells: time- and dose-dependent influence over p53 and caspase-3 protein expression and epigenetic effects. Arch. Toxicol., 91: 651–666.

Brown T.A., Lee J.W., Holian A., Porter V., Fredriksen H., Kim M., Cho Y.H. (2016). Alterations in DNA methylation corresponding with lung inflammation and as a biomarker for disease development after MWCNT exposure. Nanotoxicology, 10: 453–461.

Brzóska K., Grądzka I., Kruszewski M. (2019). Silver, gold, and iron oxide nanoparticles alter miRNA expression but do not affect DNA methylation in HepG2 cells. Materials., 12: 1038.

Choudhury S.R, Ordaz J., Lo C.L., Damayanti N.P., Zhou F., Irudayaraj J. (2017). Zinc oxide nanoparticles-induced reactive oxygen species promotes multimodal cyto- and epigenetic toxicity. Toxicol Sci., 156: 261–274.

Chouke P.B., Potbhare A.K., Meshram N.P., Rai M.M., Dadure K.M., Chaudhary K., Rai A.R., Desimone M.F., Chaudhary R.G., Masram D.T. (2022). Bioinspired NiO nanospheres: Exploring *in vitro* toxicity using Bm-17 and *L. rohita* liver cells, DNA degradation, docking, and proposed vacuolization mechanism. ACS Omega, 7: 6869–6884.

Dusinska M., Tulinska J., El Yamani N., Kuricova M., Liskova A., Rollerova E., Rundén-Pran E., Smolkova B. (2017). Immunotoxicity, genotoxicity and epigenetic toxicity of nanomaterials: New strategies for toxicity testing? Food Chem. Toxicol., 109: 797–811.

Emerce E., Ghosh M., Öner D., Duca R.C., Vanoirbeek J., Bekaert B., Hoet P.M., Godderis L. (2019). Carbon nanotube- and asbestos-induced DNA and RNA methylation changes in bronchial epithelial cells. Chem. Res. Toxicol., 32: 850–860.

Eom W., Lee E., Lee S.H., Sung T.H., Clancy A.J., Lee W.J., Han T.H. (2021). Carbon nanotube-reduced graphene oxide fiber with high torsional strength from rheological hierarchy control. Nat. Commun., 12: 396.

Fenech M. (2008). Genome health nutrigenomics and nutrigenetics diagnosis and nutritional treatment of genome damage on an individual basis. Food Chem. Toxicol., 46: 1365–1370.

Fischman M., Storey E., McCunney R.J., Kosnett M. (2011). National Institute for Occupational Safety and Health Nanomaterials and Worker Health Conference – medical surveillance session summary report. J. Occup. Environ. Med., 53: 35–37.

Francés J.L., Musolino E., Papait R., Pagiatakis C. (2023). Non-coding RNAs in cell-to-cell communication: exploiting physiological mechanisms as therapeutic targets in cardiovascular pathologies. Int. J. Mol. Sci., 24: 2205.

Gado A.R., Ellakany H.F., Elbestawy A.R., Abd El-Hack M.E., Khafaga A.F., Taha A.E., Mahgoub S.A. (2019). Herbal medicine additives as powerful agents to control and prevent avian influenza virus in poultry – a review. Ann. Anim. Sci., 19: 905–935.

Gao F., Ma N., Zhou H., Wang Q., Zhang H., Wang P., Hou H., Wen H., Li L. (2016). Zinc oxide nanoparticles-induced epigenetic change and G2/M arrest are associated with apoptosis in human epidermal keratinocytes. Int. J. Nanomed., 11: 3859–3874.

Ghanghas P., Sharma M., Desai D., Raza K., Bhalla A., Kumar P., Narula D., Amin S., Sanyal S.N., Kaushal N. (2022). Selenium-based novel epigenetic regulators offer effective chemotherapeutic alternative with wider safety margins in experimental colorectal cancer. Biol. Trace Elem. Res., 200: 635–646.

Gharpure S., Akash A., Ankamwar B. (2020). A Review on antimicrobial properties of metal nanoparticles. J. Nanosci. Nanotechnol., 20: 3303–3339.

Ghosh M., Öner D., Poels K., Tabish A.M., Vlaanderen J., Pronk A., Kuijpers E., Lan Q., Vermeulen R., Bekaert B., Hoet P.H., Godderis L. (2017). Changes in DNA methylation induced by multi-walled carbon nanotube exposure in the workplace. Nanotoxicology, 11: 1195–1210.

Ghosh M., Öner D., Duca R.C., Bekaert B., Vanoirbeek J., Godderis L., Hoet P.M. (2018). Single-walled and multi-walled carbon nanotubes induce sequence-specific epigenetic alterations in 16 HBE cells. Oncotarget, 9: 20351–20365.

Ghosh M., Godderis L., Hoet P. (2022). Epigenetic mechanisms in understanding nanomaterial-induced toxicity. In: Nanotoxicology in safety assessment of nanomaterials, Louro H., Silva M.J. (eds). Advances in Experimental Medicine and Biology, vol. 1357. Springer, Cham.

Gliga A.R., Di Bucchianico S., Lindvall J., Fadeel B., Karlsson H.L. (2018). RNA-sequencing reveals long-term effects of silver nanoparticles on human lung cells. Sci. Rep., 8: 6668.

Gong C., Tao G., Yang L., Liu J., Liu Q., Zhuang Z. (2010). SiO_2 nanoparticles induce global genomic hypomethylation in HaCaT cells. Biochem. Biophys. Res. Commun., 397: 396–400.

Gong C., Tao G., Yang L., Liu J., Liu Q., Li W., Zhuang Z. (2012). Methylation of *PARP-1* promoter involved in the regulation of nano-SiO_2-induced decrease of PARP-1 mRNA expression. Toxicol Lett., 209: 264–269.

Gupta J., Sharma S., Sharma N.R., Kabra D. (2020). Phytochemicals enriched in spices: a source of natural epigenetic therapy. Arch. Pharm. Res., 43: 171–186.

Gupta R., Xie H. (2018). Nanoparticles in daily life: applications, toxicity and regulations. J. Environ. Pathol Toxicol Oncol., 37: 209–230.

Hanot-Roy M., Tubeuf E., Guilbert A., Bado-Nilles A., Vigneron P., Trouiller B., Braun A., Lacroix G. (2016). Oxidative stress pathways involved in cytotoxicity and genotoxicity of titanium dioxide (TiO_2) nanoparticles on cells constitutive of alveolo-capillary barrier *in vitro*. Toxicol In vitro, 33: 125–135.

Hu J., Lin W., Lin B., Wu K., Fan H., Yu Y. (2019). Persistent DNA methylation changes in zebrafish following graphene quantum dots exposure in surface chemistry-dependent manner. Ecotoxicol. Environ. Saf., 169: 370–375.

Huang Y., Wu R., Su Z.Y., Guo Y., Zheng X., Yang C.S., Kong A.N. (2017). A naturally occurring mixture of tocotrienols inhibits the growth of human prostate tumor, associated with epigenetic modifications of cyclin-dependent kinase inhibitors p21 and p27. J. Nutr. Biochem., 40: 155–163.

Jiang Z., Lai Y., Beaver J.M., Tsegay P.S., Zhao M.L., Horton J., Zamora M., Rein H.L., Miralles F., Shaver M., Hutcheson J.D., Agoulnik I., Wilson S.H., Liu Y. (2020). Oxidative DNA damage modulates DNA methylation pattern in human breast cancer 1 (*BRCA1*) gene via the crosstalk between DNA polymerase *β* and a *de novo* DNA methyltransferase. Cells, 9: E225.

Johansen K.M., Johansen J. (2006). Regulation of chromatin structure by histone H3S10 phosphorylation. Chromosome Res., 14: 393–404.

Jou Y.J., Chen C.J., Liu Y.C., Way T.D., Lai C.H., Hua C.H., Wang C.Y., Huang S.H., Kao J.Y., Lin C.W. (2015). Quantitative phosphoproteomic analysis reveals γ-bisabolene inducing p53-mediated apoptosis of human oral squamous cell carcinoma via HDAC2 inhibition and ERK1/2 activation. Proteomics, 15: 3296–3309.

Kalaiarasi A., Sankar R., Anusha C., Saravanan K., Aarthy K., Karthic S., Mathuram T.L., Ravikumar V. (2018). Copper oxide nanoparticles induce anticancer activity in A549 lung cancer cells by inhibition of histone deacetylase. Biotechnol. Lett., 40: 249–256.

Kanwal R., Datt M., Liu X., Gupta S. (2016). Dietary flavones as dual inhibitors of DNA methyltransferases and histone methyltransferases. PLoS One, 11(9):e0162956.

Khafaga A.F., Abd El-Hack M.E., Taha A.E., Elnesr S.S., Alagawany M. (2019). The potential modulatory role of herbal additives against Cd toxicity in human, animal, and poultry: a review. Environ. Sci. Poll. Res., 26: 4588–4604.

Kiany T., Pishkar L., Sartipnia N., Iranbakhsh A., Barzin G. (2022). Effects of silicon and titanium dioxide nanoparticles on arsenic accumulation, phytochelatin metabolism, and antioxidant system by rice under arsenic toxicity. Environ. Sci. Pollut. Res. Int., 29: 34725–34737.

Könen-Adıgüzel S., Ergene S. (2018). *In vitro* evaluation of the genotoxicity of CeO_2 nanoparticles in human peripheral blood lymphocytes using cytokinesis-block micronucleus test, comet assay, and gamma H2AX. Toxicol. Ind. Health., 34: 293–300.

Kopp B., Dario M., Zalko D., Audebert M. (2018). Assessment of a panel of cellular biomarkers and the kinetics of their induction in comparing genotoxic modes of action in HepG2 cells. Environ. Mol. Mutagen., 59: 516–528.

Kung M.L., Hsieh S.L., Wu C.C., Chu T.H., Lin Y.C., Yeh B.W., Hsieh S. (2015). Enhanced reactive oxygen species overexpression by CuO nanoparticles in poorly differentiated hepatocellular carcinoma cells. Nanoscale, 7: 1820–1829.

Lebre F., Chatterjee N., Costa S., Fernández-de-Gortari E., Lopes C., Meneses, J., Ortiz L., Ribeiro A.R., Vilas-Boas V., Alfaro-Moreno E. (2022). Nanosafety: an evolving concept to bring the safest possible nanomaterials to society and environment. Nanomaterials, 12: 1810.

Lee KS., El-Sayed M.A. (2006). Gold and silver nanoparticles in sensing and imaging: sensitivity of plasmon response to size, shape, and metal composition. J. Phys. Chem. B., 110: 19220–19225.

Liang Z.Z., Zhang Y.X., Zhu R.M., Li Y.L., Jiang H.M., Li R.B., Chen Q.X., Wang Q., Tang L.Y., Ren Z.F. (2022). Identification of epigenetic modifications mediating the antagonistic effect of selenium against cadmium-induced breast carcinogenesis. Environ. Sci. Pollut. Res., 29: 22056–22068.

Liou S.H., Wu W.T., Liao H.Y., Chen C.Y., Tsai C.Y., Jung W.T., Lee H.L. (2017). Global DNA methylation and oxidative stress biomarkers in workers exposed to metal oxide nanoparticles. J. Hazard Mater., 331: 329–335.

Liu D., Wu D., Zhao L., Yang Y., Ding J., Dong L., Hu L., Wang F., Zhao X., Cai Y., Jin J. (2015). Arsenic trioxide reduces global histone H4 acetylation at lysine 16 through direct binding to histone acetyltransferase hMOF in human cells. PLoS One, 10:e0141014.

Liu J., Zhao Y., Ge W., Zhang P., Liu X., Zhang W., Hao Y., Yu S., Li L., Chu M., Min L., Zhang H., Shen W. (2017). Oocyte exposure to ZnO nanoparticles inhibits early embryonic development through the *γ-H2AX* and *NF-κB* signaling pathways. Oncotarget, 8: 42673–42692.

Liu X., Jiao B., Shen L. (2018). The epigenetics of Alzheimer's disease: factors and therapeutic implications. Front. Genet., 9: 579.

Long J., Ma W., Yu Z., Liu H., Cao Y. (2019). Multi-walled carbon nanotubes (MWCNTs) promoted lipid accumulation in THP-1 macrophages through modulation of endoplasmic reticulum (ER) stress. Nanotoxicology, 13: 938–951.

Lu X., Miousse I.R., Pirela S.V., Melnyk S., Koturbash I., Demokritou P. (2016 a). Short-term exposure to engineered nanomaterials affects cellular epigenome. Nanotoxicology, 10: 140–150.

Lu X., Miousse I.R., Pirela S.V., Moore J.K., Melnyk S., Koturbash I., Demokritou P. (2016 b). *In vivo* epigenetic effects induced by engineered nanomaterials: A case study of copper oxide and laser printer-emitted engineered nanoparticles. Nanotoxicology, 10: 629–639.

Lv L., Liu Y., Zhang P., Zhang X., Liu J., Chen T., Su P., Li H., Zhou Y. (2015). The nanoscale geometry of TiO2 nanotubes influences the osteogenic differentiation of human adipose-derived stem cells by modulating H3K4 trimethylation. Biomaterials, 39: 193–205.

Mehana N.A., Ghaiad H.R., Hassan M., Elsabagh Y.A., Labib S., Abd-Elmawla M.A. (2022). LncRNA MEG3 regulates the interplay between Th17 and Treg cells in Behçet's disease and systemic lupus erythematosus. Life Sci., 309: 120965.

Mira A., Shimizu K. (2015). *In vitro* cytotoxic activities and molecular mechanisms of *Angelica shikokiana* extract and its isolated compounds. Pharmacogn. Mag., 11(Suppl 4): S564–S569.

Missaoui W.N., Arnold R.D., Cummings B.S. (2018). Toxicological status of nanoparticles: what we know and what we don't know. Chem. Biol. Interact., 295: 1–12.

Musolino E., Pagiatakis C., Serio S., Borgese M., Gamberoni F., Gornati R., Papait R. (2022). The Yin and Yang of epigenetics in the field of nanoparticles. Nanoscale Adv., 4: 979–994.

Mytych J., Zebrowski J., Lewinska A., Wnuk M. (2017). Prolonged effects of silver nanoparticles on p53/p21 pathway-mediated

proliferation, DNA damage response, and methylation parameters in HT22 hippocampal neuronal cells. Mol. Neurobiol., 54: 1285–1300.

Ng C.T., Dheen S.T., Yip W.C., Ong C.N., Bay B.H., Yung L.Y.L. (2011). The induction of epigenetic regulation of *PROS1* gene in lung fibroblasts by gold nanoparticles and implications for potential lung injury. Biomaterials, 32: 7609–7615.

Öner D., Ghosh M., Coorens R., Bové H., Moisse M., Lambrechts D., Ameloot M., Godderis L., Hoet P.M. (2017). Epigenetic effects of carbon nanotubes in human monocytic cells. Mutagenesis, 32: 181–191.

Öner D., Ghosh M., Bové H., Moisse M., Boeckx B., Duca R.C., Poels K., Luyts K., Putzeys E., Van Landuydt K., Vanoirbeek J.A., Ameloot M., Lambrechts D., Godderis L., Hoet P.H. (2018). Differences in MWCNT- and SWCNT-induced DNA methylation alterations in association with the nuclear deposition. Part Fibre Toxicol., 15: 11.

Öner D., Ghosh M., Coorens R., Bové H., Moisse M., Lambrechts D., Ameloot M., Godderis L., Hoet P.M. (2020). Induction and recovery of CpG site specific methylation changes in human bronchial cells after long-term exposure to carbon nanotubes and asbestos. Environ. Int., 137: 105530.

Ooi S.K., O'Donnel A.H., Bestor T.H. (2009). Mammalian cytosine methylation at a glance. J. Cell Sci., 122: 2787–2791.

Pascoal G.L., Novaes G.M., Sobrinho M.P., Hirayama A.B., Castro I.A., Ong T.P. (2022). Selenium supplementation during puberty and young adulthood mitigates obesity-induced metabolic, cellular and epigenetic alterations in male rat physiology. Antioxidants, 11: 895.

Patil N.A., Gade W.N., Deobagkar D.D. (2016). Epigenetic modulation upon exposure of lung fibroblasts to TiO_2 and ZnO nanoparticles: alterations in DNA methylation. Int. J. Nanomed., 11: 4509–4519.

Patil Y.M., Rajpathak S.N., Deobagkar D.D. (2019). Characterization and DNA methylation modulatory activity of gold nanoparticles synthesized by *Pseudoalteromonas* strain. J. Biosci., 14: 4573–4587.

Pogribna M., Koonce N.A., Mathew A., Word B., Patri A.K., Lyn-Cook B., Hammons G. (2020). Effect of titanium dioxide nanoparticles on DNA methylation in multiple human cell lines. Nanotoxicology, 14: 534–553.

Prasad R.Y., Chastain P.D., Nikolaishvili-Feinberg N., Smeester L., Kaufmann W.K., Fry R.C. (2013). Titanium dioxide nanoparticles activate the ATM-Chk2 DNA damage response in human dermal fibroblasts. Nanotoxicology, 7: 1111–1119.

Qian Y., Zhang J., Hu Q., Xu M., Chen Y., Hu G., Zhao M., Liu S. (2015). Silver nanoparticle-induced hemoglobin decrease involves alteration of histone 3 methylation status. Biomaterials, 70: 12–22.

Romanek J. (2013). Epigenetic basis of molecular changes in animal cells with particular regard to embryonic development – a review. Ann. Anim. Sci., 13: 675–685.

Rossner P., Vrbova K., Rossnerova A., Zavodna T., Milcova A., Klema J., Vecera Z., Mikuska P., Coufalik P., Capka L., Krumal K., Docekal B., Holan V., Machala M., Topinka J. (2020). Gene expression and epigenetic changes in mice following inhalation of copper (II) oxide nanoparticles. Nanomaterials (Basel), 10: 550.

Rossnerova A., Honkova K., Pelclova D., Zdimal V., Hubacek J.A., Chvojkova I., Vrbova K., Rossner P., Topinka J., Vlckova S., Fenclova Z., Lischkova L., Klusackova P., Schwarz J., Ondracek J., Ondrackova L., Kostejn M., Klema J., Dvorackova S. (2020). DNA methylation profiles in a group of workers occupationally exposed to nanoparticles. Int. J. Mol. Sci., 21: 2420.

Saeed M., Abd El-Hack M.E., Alagawany M., Arain M.A., Arif M., Mirza M.A., Dhama K. (2017 a). Chicory (*Cichorium intybus*) herb: Chemical composition, pharmacology, nutritional and healthical applications. Inter. J. Pharm., 13: 351–360.

Saeed M., Abd El-Hack M.E., Arif M., El-Hindawy M.M., Attia A.I., Mahrose K.M., Noreldin A.E. (2017 b). Impacts of distiller's dried grains with solubles as replacement of soybean meal plus vitamin E supplementation on production, egg quality and blood chemistry of laying hens. Ann. Anim. Sci., 17: 849–862.

Saeed M., Yatao, X., Hassan F.U., Arain M.A., Abd El-Hack M.E., Noreldin A.E., Sun C. (2018). Influence of graded levels of L-theanine dietary supplementation on growth performance, carcass traits, meat quality, organs histomorphometry, blood chemistry and immune response of broiler chickens. Inter. J. Mol. Sci., 19: 462.

Sahafnejad Z., Ramazi S., Allahverdi A. (2023). An update of epigenetic drugs for the treatment of cancers and brain diseases: A comprehensive review. Genes, 14: 873.

Samiec M., Skrzyszowska M. (2018). Can reprogramming of overall epigenetic memory and specific parental genomic imprinting memory within donor cell-inherited nuclear genome be a major hindrance for the somatic cell cloning of mammals? – a review. Ann. Anim. Sci., 18: 623–638.

Schulte P.A., Leso V., Niang M., Iavicoli I. (2019). Current state of knowledge on the health effects of engineered nanomaterials in workers: a systematic review of human studies and epidemiological investigations. Scand. J. Work Environ. Health, 45: 217–238.

Seidel C., Kirsch A., Fontana C., Visvikis A., Remy A., Gaté L., Darne C., Guichard Y. (2017). Epigenetic changes in the early stage of silica-induced cell transformation. Nanotoxicology, 11: 923–935.

Semik-Gurgul E., Ząbek T., Kawecka-Grochocka E., Zalewska M., Kościuczuk E., Bagnicka E. (2022). Epigenetic states of genes controlling immune responsiveness in bovine chronic mastitis. Ann. Anim. Sci., 22: 575–581.

Setyawati M.I., Khoo P.K., Eng B.H., Xiong S., Zhao X., Das G.K., Tan T.T., Loo J.S., Leong D.T., Ng K.W. (2013). Cytotoxic and genotoxic characterization of titanium dioxide, gadolinium oxide, and poly (lactic-co-glycolic acid) nanoparticles in human fibroblasts. J. Biomed. Mater Res A., 101: 633–640.

Shyamasundar S., Ng C.T., Yung L.L., Dheen S.T., Bay B.H. (2015). Epigenetic mechanisms in nanomaterial-induced toxicity. Epigenomics, 7: 395–411.

Sierra M.I., Valdés A., Fernández A.F., Torrecillas R., Fraga M.F. (2016). The effect of exposure to nanoparticles and nanomaterials on the mammalian epigenome. Int. J. Nanomed., 11: 6297–6306.

Sima M., Vrbova K., Zavodna T., Honkova K., Chvojkova I., Ambroz A., Klema J., Rossnerova A., Polakova K., Malina T., Belza J., Topinka J., Rossner P. Jr. (2020). The differential effect of carbon dots on gene expression and DNA methylation of human embryonic lung fibroblasts as a function of surface charge and dose. Int. J. Mol. Sci., 4763.

Skrzyszowska M., Samiec M. (2020). Enhancement of in vitro developmental outcome of cloned goat embryos after epigenetic modulation of somatic cell-inherited nuclear genome with trichostatin A. Ann. Anim. Sci., 20: 97–108.

Smolkova B., Miklikova S., Horvatova K.V., Babelova A., El Yamani N., Zdurencikova M., Fridrichova I., Zmetakova I., Krivulcik T., Kalinkova L., Matuskova M., Kucerova L., Dusinska M. (2016). Global and gene specific DNA methylation in breast cancer cells was not affected during epithelial-to-mesenchymal transition *in vitro*. Neoplasma, 63: 901–910.

Sooklert K., Nilyai S., Rojanathanes R., Jindatip D., Sae-Liang N., Kitkumthorn N., Mutirangura A., Sereemaspun A. (2019). N-acetylcysteine reverses the decrease of DNA methylation status caused engineered gold, silicon, and chitosan nanoparticles. Int. J. Nanomed., 14: 4573–4587.

Stoccoro A., Di Bucchianico S., Coppedé F., Ponti J., Uboldi C., Blosi M., Delpivo C., Ortelli S., Costa A.L., Migliore L. (2017). Multiple endpoints to evaluate pristine and remediated titanium dioxide nanoparticles genotoxicity in lung epithelial A549 cells. Toxicol. Lett., 276: 48–61.

Surapaneni S.K., Bashir S., Tikoo K. (2018). Gold nanoparticles-induced cytotoxicity in triple negative breast cancer involves different epigenetic alterations depending upon the surface charge. Sci. Rep., 8: 12295.

Szczepanek J., Skorupa M., Jarkiewicz-Tretyn J., Cybulski C., Tretyn A. (2023). Harnessing epigenetics for breast cancer therapy: The role of DNA methylation, histone modifications, and microRNA. Int. J. Mol. Sci., 24: 7235.

Tabish A.M., Poels K., Byun H.M., Luyts K., Baccarelli A.A., Martens J., Kerkhofs S., Seys S., Hoet P., Godderis L. (2017). Changes

in DNA methylation in mouse lungs after a single intra-tracheal administration of nanomaterials. PLoS One, 12:e0169886.
Tarantini A., Lanceleur R., Mourot A., Lavault M.T., Casterou G., Jarry G., Hogeveen K., Fessard V. (2015). Toxicity, genotoxicity and proinflammatory effects of amorphous nanosilica in the human intestinal Caco-2 cell line. Toxicol In Vitro, 29: 398–407.
Torres I.O., Fudjimori D.G. (2015). Functional coupling between writers, erasers and readers of histone and DNA methylation. Curr. Opin. Struct. Biol., 25: 68–75.
Valinluck V., Sowers L.C. (2007). Inflammation-mediated cytosine damage: a mechanistic link between inflammation and the epigenetic alterations in human cancers. Cancer Res., 67: 5583–5586.
Valinluck V., Tsai H.H., Rogstad D.K., Burdzy A., Bird A., Sowers L.C. (2004). Oxidative damage to methyl-CpG sequences inhibits the binding of the methyl-CpG binding domain (MBD) of methyl-CpG binding protein 2 (MeCP2). Nucleic Acids Res., 32: 4100–4108.
Wan R., Mo Y., Feng L., Chien S., Tollerud D.J., Zhang Q. (2012). DNA damage caused by metal nanoparticles: involvement of oxidative stress and activation of ATM. Chem. Res. Toxicol., 25: 1402–1411.
Wu X., Zhang Y. (2017). TET-mediated active DNA demethylation: mechanism, function and beyond. Nat. Rev. Genet., 18: 517–534.
Xiaoli F., Qiyue C., Weihong G., Yaqing Z., Chen H., Junrong W., Longquan S. (2020). Toxicology data of graphene-family nanomaterials: an update. Arch. Toxicol., 94: 1915–1939.
Zhang L., Han B., Xiang J., Liu K., Dong H., Gao X. (2018). Silica nanoparticle releases SIRT6-induced epigenetic silencing of follistatin. Int. J. Biochem. Cell Biol., 95: 27–34.
Zhang T., Du E., Liu Y., Cheng J., Zhang Z., Xu Y., Qi S., Chen Y. (2020). Anticancer effects of zinc oxide nanoparticles through altering the methylation status of histone on bladder cancer cells. Int. J. Nanomed., 15: 1457–1468.
Zhao X., Takabayashi F., Ibuki Y. (2016). Coexposure to silver nanoparticles and ultraviolet A synergistically enhances the phosphorylation of histone H2AX. J. Photochem. Photobiol. B., 162: 213–222.
Zhao X., Rao Y., Liang J., Lin S., Wang X., Li Z., Huang J. (2019). Silver nanoparticle-induced phosphorylation of histone H3 at serine 10 involves MAPK pathways. Biomolecules, 9: 78.
Zhou W., Tian D., He J., Yan X., Zhao J., Yuan X., Peng S. (2019). Prolonged exposure to carbon nanoparticles induced methylome remodeling and gene expression in zebrafish heart. J. Appl. Toxicol., 39: 322–332.
Zou Y., Li Q., Jiang L., Guo C., Li Y., Yu Y., Li Y., Duan J., Sun Z. (2016). DNA hypermethylation of CREB3L1 and Bcl-2 associated with the mitochondrial-mediated apoptosis via PI3K/Akt pathway in human BEAS-2B cells exposure to silica nanoparticles. PLoS One, 11:e0158475.
Zuo Q., Wu R., Xiao X., Yang C., Yang Y., Wang C., Lin L., Kong A.N. (2018). The dietary flavone luteolin epigenetically activates the Nrf2 pathway and blocks cell transformation in human colorectal cancer HCT116 cells. J. Cell Biochem., 119: 9573–9582.

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