Review Article:
Involvement of Epigenetics in the Pathogenesis, Testing and Management of Coronavirus Disease 2019 (COVID-19) Pandemic: A Narrative Review

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ABSTRACT

Background: There is an intense search for the Coronavirus Disease 19 (COVID-19) cure, to stem the spread and burden of the disease worldwide. Studies revealed that epigenetic modifications impact the pathogenesis of some COVID-19 cases, which can be used as therapeutic targets.

Objectives: This review articulated the role of epigenetics in the pathogenesis and management of COVID-19.

Methods: Relevant articles published between January 2000 and November 2020 were retrieved from reputable academic databases, including PubMed, SpringerLink, Scopus, and Google Scholar.

Results: Epigenetic modifications in the COVID-19’s pathogen, called the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and host’s cells may influence susceptibility or resistance to the disease. Notably, abnormal Deoxyribonucleic Acid (DNA) methylation and histone modification involving immune regulatory genes and molecules, such as cytokines and interferon-regulated genes may compromise immune function and enhance the host’s susceptibility and disease severity. The hypomethylation of SARS-CoV-2’s receptor, called the Angiotensin-Converting Enzyme 2 (ACE2), causing its overexpression, can also enhance SARS-CoV-2’s infectivity. Moreover, SARS-CoV-2 can hijack the host’s MicroRNA (miRNA) using its miRNA and compromise the immune function, increasing its infectivity. Fortunately, epigenetic changes are reversible; thus, a therapy that targets the epigenetic changes in the affected case may reverse COVID-19.

Conclusion: Modifications in the SARS-CoV-2 or host epigenome promote the pathogenesis and severity of COVID-19. Epigenetic changes are reversible, so healthcare providers are advised to formulate therapeutic procedures that target the causal mechanisms in the affected individual.
Introduction

Coronavirus Disease 2019 (COVID-19) broke out in December 2019 and shortly spread across several countries, leading to high mortality worldwide [1]. The causative agent of COVID-19 is Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a member of the genus Betacoronavirus [2]. The virus is related to SARS-CoV and the Middle East Respiratory Syndrome (MERS-CoV) [3]. However, SARS-CoV-2 has a lower mortality rate (2.3%), compared to SARS-CoV (9.5%) and considerably lower than that of MERS-CoV (34.4%) [2]. The relatively low severity of SARS-CoV-2 may explain its easy and rapid spread among individuals, compared to MERS-CoV and SARS-CoV [2]. The symptoms of COVID-19 are mainly related to the respiratory system; most patients may return to normal without requiring special treatment [1]. Older people and those with underlying medical problems, such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more prone to develop serious COVID-19 [1]. There is also increasing evidence that numerous COVID-19 patients may remain asymptomatic [4].

COVID-19 pandemic caused a global lockdown of activities, which affected national budgets and businesses, and nearly caused an economic meltdown in some countries. These conditions have led to an intense search for the relevant vaccines and drugs, to reduce the spread of the virus and cure the infected. Some studies suggested that epigenetic modifications in individuals and SARS-CoV-2 genomes contribute to the virus’s pathogenesis. Epigenetic modifications are heritable changes in gene expression and function without altering the genetic makeup [5]. Epigenetic changes may alter the expression of genes involved in immune response as well as the viral genome, predisposing to or protecting from infection [6]. Thus, understanding the mechanisms by which SARS-CoV-2 epigenetically hijacks the cellular apparatus may help develop vaccines and therapeutic procedures. Accordingly, this review articulated epigenetic mechanisms in the host and viral genomes involved in the pathogenesis of COVID-19, as well as potential epigenetic drugs.

Materials and Methods

Database searching and search strategy

Academic databases searched for relevant information included PubMed, SpringerLink, Scopus, Google Scholar, and Semantic Scholar. Selected search terms used to retrieve articles consisted of “epigenetics, epigenetic mechanisms, coronavirus diseases, coronavirus disease 2019, pathology of COVID-19, SARS-CoV-2, epigenetic testing, and viral infections”. Other applied search terms included “the role of DNA methylation in COVID-19, the role of histone modification in COVID-19, the role of non-coding RNAs in COVID-19, and epigenetic drugs”. The articles collected from each database were pooled together and duplicates were removed using EndNote.

Criteria for the inclusion and exclusion of articles

Included articles were in English with a focus on the epigenetic aspects of COVID-19. Furthermore, only articles published from January 2000 to November 2020 were included. Excluded articles consisted of those without available full texts and those that failed to meet the above-mentioned inclusion criteria.

Seventy-Five articles were retrieved from the searched databases (Figure 1). However, after removing duplicates, 68 articles were retained. The 68 articles were subjected to an eligibility test and 60 articles scaled through. Of the 60 articles, 53 focused on the study aim; thus, made the final selection.

Mechanistic links between epigenetics and COVID-19

Epigenetics is described as the study of genetic and non-genetic factors that control phenotypic variations [7]. Epigenetic modifications turn genes on or off; thus, altering the expression or function of the genes without altering the genetic constitutions [7, 8]. Epigenetic processes are necessary for healthy cellular activities, such as growth and development. However, changes in genes that ideally protect against certain diseases could make individuals more susceptible to diseases [8]. Characteristics that can induce epigenetic changes include certain diets and environmental chemicals [8]. Microorganisms, such as hepatitis B and Epstein-Barr Virus (EBV), as well as intracellular bacteria, can also epigenetically manipulate the host cells to enhance their maintenance, replication, and transmission [9]. Coronaviruses are suspected to alter the human epigenome, allowing them to bypass the host’s immune system and successfully mount and spread infection [6, 7]. Three major epigenetic mechanisms through which microorganisms, including coronaviruses, can manipulate the host epigenome to establish an infection are Deoxyribonucleic Acid (DNA) methylation, histone modifications, and non-coding RNA-associated gene silencing [10]. Articles that focused on the
mechanistic links between epigenetics and COVID-19 are summarized in Table 1.

The role of DNA methylation in COVID-19 pathogenesis

DNA methylation is an epigenetic mechanism involving the addition of a methyl group to a cytosine residue in a Cytosine-guanine Sequence (CpG) [10]. There exist clusters of CpG sites in the cells (i.e., CpG island) whose methylation in a gene promoter may silence the gene [10]. The binding of methyl groups is modulated by a group of enzymes collectively called DNA Methyltransferases (DNMTs), which include DNMT1, DNMT2, DNMT3a, DNMT3b, and DNMT3L [5, 10]. DNA methylation is involved in microbial infection, of which, the abnormal methylation of certain genes involved in infection mounting and immune response may enhance viral infection. Some microbes may also epigenetically manipulate the host cell to enhance infectivity. SARS-CoV-2, in particular, invades the host cells by attaching to a receptor encoded by a gene, called Angiotensin-Converting Enzyme 2 (ACE2). However, the binding affinity of the virus depends on the methylation and expression of ACE2, i.e., influenced by the functional state of the immune system.

The immune function is influenced by age, health status, gender, and even the genome of SARS-CoV-2. The differential methylation and expression of ACE2 in individuals may therefore be partly responsible for the variations observed in COVID-19 vulnerability. Hypermethylation increases the expression and virus binding ability of the ACE2, while hypomethylation decreases it. Diseases (health status), particularly immune-mediated diseases, can cause hypomethylation of the ACE2, resulting in its overexpression and increased affinity for SARS-CoV-2.

Table 1. Mechanistic links between epigenetics and COVID-19

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>References</th>
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<tbody>
<tr>
<td>DNA methylation</td>
<td>5, 10, 11, 12, 13, 14, 15, 16, 17, 18</td>
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<tr>
<td>Histone post translational modification</td>
<td>5, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26</td>
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<tr>
<td>Non-Coding RNA* gene silencing</td>
<td>10, 27, 28, 29, 30, 31, 32, 33</td>
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* RNA: Ribonucleic Acid
The hypomethylation of ACE2 in diseased individuals may be further aggravated by a viral infection. For example, Sawalha et al. [11] indicated that oxidative stress caused by SARS-CoV-2 exacerbated the hypomethylation of ACE2-induced lupus, increasing the odds of infection.

Females are prone to encounter the effects of disease-mediated hypomethylation of ACE2. This is because the reduced DNA methylation may cause a defective X chromosome inactivation [12]. This may further upregulate X-linked genes, which include the ACE2. DNA methylation is essential for inactivating the X chromosome in which expressing one copy of the X chromosome in females is repressed [11]. This is necessary to maintain the normal expression level of female cells, comparable to male cells [11]. In a study of COVID-19 patients by Corley and Ndhlou [13], DNA methylation analysis at two CpG sites related to the ACE2 gene suggested that female subjects were significantly hypomethylated, compared to males [13]. This could have resulted from the disruption of inactivation of the X chromosome, upregulating its genes, including the gene that codes for ACE2; thus, culminating in increased susceptibility to COVID-19.

Aside from ACE2, immune-related diseases, like lupus may cause the demethylation of interferon-regulated genes, like the nuclear factor kappa light chain enhancer of activated B cells (NFκB), as well as certain cytokine genes [11]. The demethylation of these genes may cause an overreaction of the immune response to SARS-CoV-2, resulting in cytokine storm [11]. A cytokine storm may induce autoimmunity, leading to cell death and organ failure [14]. Multiple other immune-mediated diseases may produce similar effects as lupus. For example, Chai et al. [15] observed the hypomethylation and overexpression of ACE2 in COVID-19 patients expressing different tumor types. Other members of the coronavirus family, such as MERS-CoV and SARS-CoV, as well as H5N1 influenza, have been manifested to compromise the immune function through DNA methylation and histone modifications to mount infections [16]. Additionally, SARS-CoV uses ACE2 as the receptor and can epigenetically induce overexpression of the receptor to cause infection [17]. Collectively, these data revealed that epigenetic modifications may promote viral entry, infectivity, abnormal immune reactions to SARS-CoV-2, and severe COVID-19 [11, 14].

Regarding aging, it may cause the hypomethylation of ACE2 through immune function decline, compromising viral defenses, including adaptive immune memory [18]. The methylation of the CpGs in the ACE2 promoter declines with age [18], which could overexpress the ACE2 gene and increase its viral binding affinity. In a genome-wide DNA methylation study of freshly isolated airway epithelial cells of non-asthmatics SARS-CoV-2 patients, the levels of methylation of a CpG site (cg08559914) near the ACE2 gene correlated with biological age [13]. Furthermore, RNA sequences from the lungs of young males presented significantly low methylation and high levels of transcription, compared with fetal and female lungs [13]. Thus, the decreasing methylation of ACE2 as aging progress could partly explain while most elderly manifest a more severe form of COVID-19 [13]. Coronaviruses may facilitate the aging of the immune system through epigenetic alterations, enhancing the virus’s infectivity [18]. MERS-CoV, for instance, may compromise host antigen presentation by disrupting DNA methylation, silencing genes that encode major histocompatibility complexes [18].

The role of histone modifications in COVID-19 pathogenesis

Histones are the major proteins (called chromatin) in the chromosome that condense and help package DNA in the chromosomes [19]; thus, histone modifications may affect numerous biological processes. Histone modifications are changes in the chromatin structure that may alter the expression and function of the embedded genes [20]. The histone’s N-termini, called histone tails, extend from the globular protein unit, making the tails the targets for histone modifications [21]. Mechanisms that can modify histones include acetylation, methylation, phosphorylation, and ubiquitylation [5]. However, acetylation and methylation are the most frequent histone modifications [5]. The enzymes that catalyze histone acetylation and methylation are Histone Acetyltransferases (HATs) and Histone Methyltransferases (HMTs), while Histone Deacetylases (HDACs) and Histone Demethylases (HDMs) catalyze deacetylation and demethylation, respectively [20]. In humans, factors that can modify histones include diets, chemicals, pathogens, as well as diseases, and aging [16]. Certain diseases may modify the histone, upregulating the ACE2 and increasing COVID-19 susceptibility. In a study that compared lung transcriptomes in individuals with comorbidities related to severe COVID-19, such as diabetes mellitus and vascular diseases, ACE2 was overexpressed in the individuals, compared to the non-affected individuals [22]. Notably, the analyses revealed histone modification, which upregulated ACE2-related genes, such as Histone Acetyltransferase 1 (HAT1), Histone Deacetylase 2 (HDAC2), and Lysine Demethylase 5B (KDM5B) [22]. This finding suggested that individuals with such diseases may experience a high odds of expressing severe COVID-19.
There is a dearth of literature on the histone-modifying activities of SARS-CoV-2. However, some studies documented highly pathogenic viruses, including the coronavirus may induce the loss of the antiviral functions of interferon-regulated genes within the host by repressing the histone, enhancing infection. A study compared the interferon-regulated gene response patterns following Asian avian influenza (H5N1 & HPAI), SARS-CoV, and MERS-CoV infections.

The relevant data suggested that the viruses used similar approaches to antagonize the global interferon-regulated gene response [23]. The viruses induce repressive histone modifications, which downregulate interferon-regulated genes’ expression [23]. Another study analyzed the epigenetic changes following influenza infection; accordingly, the hypoacetylation of the histone was observed [24]. The epigenetic changes inactivate embedded genes, enhancing influenza virus infection [24]. Particularly, the influenza virus induces the hypomethylation of histone H3 lysine 79 (H3K79), which increases the virus’ replication. In the same study, the methylation of H3K79 was demonstrated to control the replication of the influenza virus and some other potent interferon-disrupting viruses [24]. Thus, H3K79 methylation may help control interferon disruption by viral pathogens [24]. Furthermore, SARS-CoV was suggested in a study to change histone methylation, accompanied by the overreaction of interferon-response genes [18]. SARS-CoV-2, being genetically similar to SARS-CoV, may likely induce a similar immune response.

Aging may accelerate histone modification, declining immune function, and promoting infectivity. Changes in chromatin are increasingly linked with cellular and organismal aging in several species [25]. Immune cells from young individuals possess a strong and healthy chromatin structure protected from damage by long telomeres and compacted heterochromatin [25]. Furthermore, chromatin in aged cells, expresses shortened telomeres, disrupted epigenome, and loose heterochromatin [25].

Data on age-related genome-wide changes in histone modifications in mammalian cells are scarce. However, the RNA sequence of the mouse germ cell line manifested histone modification, which reduced histone H3 lysine 27 trimethylation (H3K27me3) and upregulated ACE2 expression. A similar observation was documented in human embryonic stem cells in which ACE2 was overexpressed in the absence of the enhancer of zeste homolog 2 (EZH2), the major enzyme catalyzing H3K27me3 [26].

The role of Non-coding RNAs in COVID-19 pathogenesis

Non-Coding RNAs (ncRNAs) are functional RNA molecules, i.e., transcribed from DNA but not translated into proteins [10]. Non-Coding RNAs include miRNA, Small Interfering RNA (siRNA), Piwi Interacting RNA (piRNA), and Long Non-Coding RNA (IncRNA) [10]. Non-coding RNAs control gene expressions at transcriptional and post-transcriptional stages [10]. However, not all ncRNAs are involved in epigenetic modifications [10]. Those that affect epigenetic modifications can be classified into the short ncRNAs (<30 nucleotides) and the long ncRNAs (>200 nucleotides) [10]. The short ncRNAs can be divided into 3 subgroups of miRNAs, siRNAs, and piRNAs.

RNA post-transcriptional modifications by ncRNAs play critical roles in the life cycles of certain viruses, including human coronavirus [27]. Adenosine methylation in particular, such as N6-Methyladenosine (m6A), N6-adenosine methylase (m6Am), and 2’-O-methylation (2’-O-me) were reported to affect the viability of specific RNA viruses such as coronaviruses [27]. Adenosine methylation modulates viral cap structures, viral replication, innate sensing pathways, and the innate immune response [27]. Moreover, coronaviruses and other virus species encode their methyltransferase for self-methylating adenosine residues, promoting immune evasion [27]. This makes the viral epitranscriptome an attractive target for therapeutic intervention [27]. N6-Methyladenosine is the most common and abundant eukaryotic RNA modification, accounting for >80% of all RNA methylations [27]. N6-Methyladenosine exhibits pro- and anti-viral activities, depending on the virus species and host cell type [27]. The RNA genome of SARS-CoV-2 contains >50 potential m6A sites and ≥0.64% of alladenosines, or 0.18% of all bases, in SARS-CoV-2 RNA could be m6A [27]. The gain or loss of m6A can cause significant functional changes to RNA viruses, altering host cell fusion/entry, replication, transmission, pathogen intensity, and immune evasion [27]. The m6A epitranscriptome of host cells influences host resistance and can undergo alterations after viral infection [27]. Accordingly, epigenetic drugs and therapies that target viral and host m6A modifications may control RNA viral infection, including COVID-19, in patients expressing epigenetic changes [27].

Several studies revealed that the miRNAs of the host may attach to the genomes of the RNA virus to prevent the translation and replication of the virus [28]. Sometimes, the host may induce changes in miRNA expression, increasing its antiviral effects or activities; thus,
decreasing viral replication [28]. However, some RNA viruses can change the expression of the host miRNAs, repressing the host transcriptome, culminating in increased viral infectivity [28]. For instance, the influenza virus was introduced to repress host miR-24, increasing furin protease levels as well as the virus’s replication [29]. Furthermore, miR-146a-5p overexpression following a coronavirus infection of human hepatocytes enhanced the virus’s replication and infectivity [30]. In a study that sequenced lung samples from SARS-CoV and influenza virus-infected mice by Peng et al. [32], the differential expression of several small ncRNAs, including miRNAs (small nucleolar RNAs) were observed. Collectively, viruses encode miRNAs that control the expression of both human and viral genes, contributing to the pathogenicity of viruses [32].

In a genome scanning of SARS-CoV-2, viral and human miRNAs, as well as targets and biological processes involved in the pathogenesis of the virus, were established. Host immune response and epigenomes are the main cellular processes regulated by the miRNAs of SARS-CoV-2 [33]. It was observed that human miR-4661-3p targets the S gene of SARS-CoV-2 to control it. However, SARS-CoV-2 miRNA MR147-3p enhances the expression of transmembrane serine protease 2 (TM-PRSS2) genes, increasing SARS-CoV-2 infection. As a result, the virus genome can hijack host miRNA to compromise host biological processes involved in immune response [33]. A virus can suppress the RNA-interference pathway of the host by using viral miRNA or proteins to target cellular or viral transcripts [32].

Epigenetic tests for COVID-19

There exist epigenetic tests that can accurately detect epigenetic modifications caused by SARS-CoV-2. According to Karow [34], and epigenetic test that detects epigenetic changes in DNA from blood samples was developed by researchers from some medical institutions, notably Mount Sinai’s Icahn School of Medicine. The test detects disease-specific DNA methylation changes, which can be used to detect SARS-CoV-2 early. Interestingly, the new epigenetic test gives an appropriate COVID-19 diagnosis where genetic tests, such as exome sequencing and microarrays are ineffective [34]. Researchers and clinicians can also use the methylation profiling provided by the epigenetic test to distinguish severe cases from mild ones [34].

Some applications have also been developed which can help clinicians efficiently detect SARS-CoV-2, determine the risks and severity of COVID-19, and can be used to personalize treatment for patients. For instance, a company known as Diagenode offers tools, such as Megaruptor 3 and MicroPlex Library Preparation for sample preparation to sequence IGH/MHC immunology gene regions [35]. The company also produces RRBS/WGBS/MeDIP kits and histone modification antibodies and ChIP kits for global methylation and histones/chromatin modifications detection, respectively [35]. Generally, these tools can help detect DNA methylation alterations induced by SARS-CoV-2, i.e., effective to conduct large human cohort studies [35]. The tools can also characterize genomic regions that are involved in the immune response to SARS-CoV-2, to determine the severity of the disease. Furthermore, the tools can characterize the viral genome, to understand viral mutations [35].

Potential epigenetic drugs for COVID-19

There is no specific epigenetic drug or preparation for COVID-19. However, epigenetic mechanisms are similar in all cellular activities and disease pathologies; therefore, some epigenetic drugs formulated for other diseases may be effective in managing COVID-19. COVID-19 induced by the overexpression of ACE2 due to DNA hypomethylation can be reversed or reduced by methyl-adding epigenetic drugs. Methyl donating compounds, such as folate may reverse hypomethylation in COVID-19 patients and normalize the expressions of ACE2 [36]. Folate is a water-soluble B vitamin, i.e.,

Table 2. The potential epigenetic drugs for COVID-19

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<tr>
<th>Epigenetic Drugs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyl-adding epigenetic drugs</td>
<td>36, 37, 38, 39, 40</td>
</tr>
<tr>
<td>I-BET151</td>
<td>5, 41, 42</td>
</tr>
<tr>
<td>Oligonucleotides (anti-miRNAs)</td>
<td>43, 44, 45, 46, 47</td>
</tr>
<tr>
<td>Histone inhibitors</td>
<td>48, 49, 50, 51, 52, 53</td>
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known to boost DNA methylation and epigenetic configuration [37]. Other compounds that contain a methyl group include methionine, choline, betaine, and vitamin B-12 [38, 39]. Alternatively, hypomethylation can be reversed by blocking the enzyme that catalyzes it, called Ten-Eleven Translocation (TET) [40].

In cases where the virus compromises the immune function and upregulates the immune cells, like cytokines, causing an inflammatory response and cytokine storms, some epigenetic drugs may neutralize or repress the immune cells. Some epigenetic drugs have been developed along this line, notable among which is an epigenetic drug known as I-BET151 [5]. The drug was developed by researchers at Harvard Medical School and GlaxoSmithKline and was demonstrated to repress over-reactive cytokines, macrophages, T cells, among several immune cells [41, 42]. The drug does these by deactivating NFkB-mediated genes. I-BET151 also boosts the expression of some anti-inflammatory molecules [42].

For COVID-19 induced by the overexpression of viral miRNAs due to hypermethylation, complementary single-stranded oligonucleotides otherwise called anti-miRNAs can be used to suppress the virus’s infectivity [43]. The hypomethylation of the host miRNAs makes it to be susceptible to SARS-CoV-2; it can also be normalized by adding RNA molecules analogous to the precursors of the target miRNA or adding oligonucleotides that mimic the mature form of the miRNA of interest [44]. Some proven anti-miRNAs include Locked Nucleic Acid (LNA), antagonirs, morpholinos, byetta, victoza, trulicity, janu-via, onglyza, and tradjenta [45-47].

Histone post-translational modification is performed by some enzymes, such as Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs). Thus, for COVID-19 that initiates with histone modification, blocking, or deleting these enzymes may be helpful [48, 49]. Some common histone inhibitors which have been tested on some diseases, such as cancers and diabetes are RGFP966, vorinostat, romidepsin, and belinostat [50, 51]. Several dietary substances are under investigation as potential HDAC and HAT inhibitors. In particular, sulforaphane (an isothiocyanate isolated from broccoli sprouts) and diallyl disulf-ide (an organosulfur compound in garlic), was demonstrated to act as HDAC inhibitors [52, 53]. Table 2 presents a brief recap of potential epigenetic drugs for COVID-19.

**Conclusion**

The current review study established that epigenetic modifications in the human and SARS-CoV-2 genome impact COVID-19 pathogenesis. Alterations in epigenetic mechanisms, such as DNA methylation, histone modification, and non-coding RNAs may compromise the immune system and enhance host susceptibility to COVID-19. The alterations may also overexpress the virus’s receptor, known as ACE2, increasing the virus’ binding affinity and infectivity. These alterations may be induced by the virus’s genome or the host’s cellular processes, such as aging and certain diseases. Thus, the elderly and diseased are more susceptible and often expressed a more severe form of COVID-19. Epigenetic mechanisms are reversible and, as such, a therapeutic strategy that targets the epigenetic mechanisms that modulated COVID-19 in the affected individuals may reverse the disease.

**ethical considerations**

**Compliance with ethical guidelines**

There were no ethical considerations to be considered in this research.

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**Authors’ contributions**

Conceptualization and Supervision: Tajudeen Yahaya; Methodology: Tajudeen Yahaya and Esther Oladele; Investigation, writing, Original draft, review and editing: All authors; Data Collection: Aminu Mohammed, Abdulhakeem Haruna, and Usman Liman; Data Analysis: Aminu Mohammed, Abdulhakeem Haruna, and Usman Liman.

**Conflict of interest**

The authors declared no conflict of interest.

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