Adenomatoid odontogenic tumor (AOT) is a relatively rare benign, epithelial tumor of odontogenic origin. There is varying class of thoughts contemplating this lesion to be a hamartoma or neoplastic growth of odontogenic epithelium. Controversy regarding the histogenesis of the lesion is plentiful in earlier literature. The recent advent of immunohistochemical and ultrastructural studies has aided in throwing light on the tissue of origin of this tumor. This review aims at understanding the evolving concepts of histogenesis of AOT to better understand the biological behavior of the lesion. The review of AOT was carried out using PubMed and Google Scholar databases and 39 articles from the year 2001 to 2016 which contributed to the histogenesis of AOT were included for review. Since the origin of the cystic lining is similar to a reduced enamel epithelium and not the dental lamina, we propose the former to be the progenitor of AOT. Furthermore, we consider extra-follicular, as well as peripheral AOTs, originate from the remnants of Hertwig’s epithelial root sheath (epithelial rests of Malassez), which complies with the common histology for all these variants.

Keywords: Adenomatoid odontogenic tumor, Odontogenic tumor, Histogenesis.

INTRODUCTION

Odontogenic tumors are defined as a spectrum of lesions ranging from benign and malignant neoplasms to dental hamartomas; formed generally in the same sequence as in normal tooth development and all arising from dental remnants, that is, derived either from epithelial, ectomesenchymal and/or mesenchymal elements of the tooth-forming apparatus [1]. Knowledge of the basic elementary characters of different odontogenic tumors such as site of occurrence, age distribution and radiographic appearance is important in arriving at a clinical differential diagnosis [2,3]. Odontogenic tumors like any other neoplasm can mimic its cell of origin histologically [2,4]. The epithelium contributing to odontogenic tumor may be derived from the pre/post functional dental lamina, basal cell layer of the gingival epithelium, dental papilla/follicle, and remnants in the periodontal ligaments [5,6].

Adenomatoid odontogenic tumor (AOT) is a relatively rare, deviant, hamartomatous, benign, epithelial lesion of odontogenic origin [7], and constitutes about 2–7% of odontogenic cysts and tumors combined [5]. The WHO classification of odontogenic tumors has defined AOT as being comprised of odontogenic epithelium in an array of histoarchitectural patterns, embedded in mature connective tissue stroma, and characterized by gradual but progressive growth [8] with generally no tendency of recurrence. AOT is generally intraosseous, primarily in the anterior maxilla; the lower and upper canine area has more affinity to this lesion; however, it can also be seen in peripheral locations. More commonly seen in young patients, females are affected twice as commonly as males with a ratio of 1.1:9 [9]. AOT is a non-invasive tumor and recurrence rate is very low [10]. Different types or variants of AOT are central (or intraosseous) variants which are further divided into follicular (or pericoronal) type and extrafollicular (or extracoronal) type and the peripherin (or gingival) variant (PAOT) [11]. AOT could remain intraosseous or peripherin in the jaw bones, depending on the spatial position of the tumor and associated tooth. In deeper impacted teeth, there would be more possibility of AOT to be intraosseous follicular or extrafollicular (in the case of tooth eruption) lesion. In tooth impactions next to the alveolar ridge, the tumor could occasionally involve the gingiva during or after the eruption process, which would justify the peripheral variant [12,13].

The review of AOT was carried out using PubMed and Google Scholar databases. The keywords used were (AOT, histogenesis, odontogenic tumors, and histology) and all articles were taken for initial evaluation. Review articles on AOT and case reports on other odontogenic tumors other than AOT were excluded from the search. We also excluded clinical trials and animal research. In the present review, we studied the following 39 articles from the year 2001 to 2016 which contributed to the histogenesis of AOT were included for review (Table 1) [8,12,14-19,25-32,35-51]. The earlier articles were excluded since no significant research on histogenesis was available before this year, and earlier concepts were already addressed in articles included for this study. The purpose of this review was to delineate the clinical, histopathological, and immunohistochemical (IHC) profile of AOT to aid its diagnosis and alleviate confusion between other tumors in this category.

There are legitimate reasons for characterizing and renaming an entity, and foremost among these is when it can be established that it behaves and can be managed differently from other members of its original group. In most cases, it will be recognized as having distinguishable histopathological features also [33]. Thus, it becomes a new clinicopathological entity. The extensive review of literature of AOT has been enlisted in Table 1. This was how the AOT emerged from the then variants of ameloblastomas [34].

WHY AOT WAS CLASSIFIED AS EPITHELIAL TUMOR?

Based on the classification of odontogenic tumors that are based on the inductive influences between epithelial and mesenchymal tissues during odontogenesis, AOT has been included in the epithelial category rather than the mixed group, despite the presence of abnormal hard tissue elements within the tumor [52,53]. This was supported in a recent IHC study that used bone morphogenetic protein (BMP) to divide odontogenic tumors into those that were purely epithelial (i.e., negative for BMP) and those that formed hard tissue (i.e., positive for BMP) [54]. The epithelial component of this tumor is cellular where the pre-ameloblast like cells are arranged radially with interspersing spindle-shaped cells in some areas, whereas the other areas show epithelial cells which are arranged in interlacing strands resembling that of pleomorphic ameloblastomas [55,56].

Hamartoma or neoplasm

There is two class of thought, while some contemplate this lesion as a developmental outgrowth or hamartoma, other groups account them
| S. No. | Author/year | Age Gender | Site | Clinical features | Histopathological features | Special investigations | Concept proposed |
|-------|-------------|------------|------|-------------------|--------------------------|-----------------------|------------------|
| 1.    | Takahashi et al. 2001 [14] | 22 years old male | Maxilla | Lesion expanding to sinus | Positive staining for iron-binding proteins (transferring, ferritin) and protease inhibitor (alpha-one-antitrypsin) in various cells of AOT indicating their role to the pathogenesis of AOT. CK7 CK13 CK14 CK18 CK19 vimentin laminin collagen IV PCNA p53 | Detected the neoplastic nature of AOT by immunohistochemistry. |
| 2.    | Crivelini et al. [15] | Archival blocks used | Paraffin sections of formalin-fixed tissue were used for both histological and immunohistochemical evaluation. | - | - | Adopted the hypothesis of AOT being a simple hamartoma, whose histogenesis would be related to the reduced enamel epithelium |
| 3.    | Batra [16,35] | 17 years old female | Right mandibular canine region | Associated with an impacted canine | Ductal lamina surrounded by epithelial cells filled with eosinophilic material | Well circumscribed radiolucency | A rare case of AOT in the lower jaw |
| 4.    | Handschel et al. 2005 [36] | 23 years old male | Right mandibular canine region | Associated with an impacted canine | Whorls, sheets and plexiform arrangement of cells, duct-like structures with calcifications. | Well defined radiolucency | Rare case with respect to the age of the patient and the localization of the AOT in the lower jaw. |
| 5.    | Motamedi et al. 2005 [37] | 13 years old female | Left mandibular canine region | Associated with an impacted canine | Rosettes of spindle-shaped epithelial cells with duct-like structures | Well-defined radiolucency | Describes the treatment of an impacted mandibular canine associated with an AOT. |
| 6.    | Nigam et al. 2005 [38] | 15 years old female | Left maxillary incisor to pre-molar region | Associated with an impacted canine | Nests, cords, and ducts of epithelial cells with eosinophilic amyloid-like material | Well defined radiolucency, root resorption | Suggested that AOT should be considered in the differential diagnosis of radiolucent jaw swellings. |
| 7.    | Vargas et al. (2006) [39] | 16 years old male | Left mandibular region | Associated with an impacted canine | Odontogenic hard and soft tissues, similar to a dental germ was seen. Dental papilla and dentin were seen. Whorled nests of odontogenic epithelium with calcified basophilic spherules, irregular hyaline, and amorphous deposits | Well defined unilocular radiolucency with discrete areas of radiopacities nuclear positivity for p63, limited Ki-67 positivity, Absence of reactivity for hormonal receptors (RE and Rpg) | Proposed the term adenomatoid odontogenic hamartoma. |
| 8.    | Vera Sempere et al. 2006 [40] | 9 years old female | Left mandibular canine region | Associated with an impacted canine | Islands and sheets of globular cells with duct-like structures, amorphous eosinophilic material, and calcified areas | Well defined radiolucency with radiopaque areas | AOT revealed a scant proliferative activity. Excluded a possible hormone dependence in AOT that could explain the observed female predominance. |
| 9.    | Nonaka et al. 2007 [41] | 13 years old female | Left maxillary canine to pre-molar region | Associated with an impacted canine | Islands and sheets of globular cells with duct-like structures, amorphous eosinophilic material, and calcified areas | Well defined radiolucency with radiopaque areas | AOT associated with dentigerous cyst. |
| 10.   | Cawson et al. 2007 [12] | 16 years old female | Left mandible | Associated with an impacted tooth | Rosettes of spindle-shaped epithelial cells with duct-like structures | Well defined radiolucency | Adenomatoid odontogenic tumor in the third molar region of the mandible. |
| 11.   | Jhan et al. 2007 [42] | 40 years old male | Right mandibular premolar to molar region | No associated impacted teeth | Clusters and strands of cuboidal cells arranged in a lace-like pattern with hyaline material | Well defined radiolucency with root resorption | They suggested (AOT) to originate from the reduced enamel epithelium of the dental follicle. |

Table 1: Histogenesis of AOT (Contd...
| S. No. | Author/year | Age Gender | Site | Clinical features | Histopathological features | Special investigations | Concept proposed |
|-------|-------------|------------|------|-------------------|---------------------------|------------------------|------------------|
| 12.   | Santos et al. 2008 [43] | 22 years old male | Left anterior maxilla | No associated impacted tooth. No associated impacted teeth | Odontogenic epithelium with oval, angular, elongated cells forming a cribriform pattern | Unilocular radiolucency | Unusual presentation was a cribriform pattern in AOT. Described it as Adenomatoid dentinoma. |
| 13.   | Kemp et al. 2008 [44] | 15 years old female | Left mandibular molar region | Associated with impacted canine, unusual rapid growth | Cells arranged in whorl-like, ductular, ribbon-like, and ribon-like patterns with bands of eosinophilic material | Ill-defined radiolucency with radiopaque foci | Supported its aggressive and neoplastic nature. |
| 14.   | Garg et al. 2009 [8] | 20 years old female | Right maxillary incisor or premolar region | Swelling associated with impacted canine | Peripheral strand of smaller cells which form net-like proliferations | Immunoreactivity for cytokeratins, vimentin, and p63, and was focally immunoreactive for alpha-smooth muscle actin and epithelial membrane antigen | Adenomatoid odontogenic tumor of maxillary sinus, and pointed its neoplastic and aggressive nature. |
| 15.   | Fredrich et al. 2009 [18] | 16 years old male | Left maxillary alveolar region | | | | |
| 16.   | Carlos-Bregni et al. 2009 [45] | 19 years old female | Left mandibular molar region | No associated impacted teeth | Cuboidal cells resembling ameloblasts and stellate reticulum, the presence of enamel matrix overlying dentin | Unilocular radiolucency | Suggested (AOT) to originate from the reduced enamel epithelium of the dental follicle. |
| 17.   | Carlos-Bregni et al. 2009 [45] | 13 years old female | Left mandibular molar region | No associated impacted teeth | Globular dentin, enamel matrix, stellate reticulum, odontogenic epithelium | Unilocular radiolucency | |
| 18.   | Iide 2009 [46] | 22 years old female | Right mandibular premolar region | No associated impacted teeth | Tubular and duct-like structures, globular calcifications | Unilocular radiolucency with snow-flake-like radiopacities | |
| 19.   | Martinez et al. 2009 [47] | 10 years old female | Left mandibular molar region | No associated impacted teeth | Rosette and duct-like structures with intercellular eosinophilic material, calcified masses of tubular dentin and dentinoid material with enamel matrix foci | Unilocular radiolucency with radiopaque mass | |
| 20.   | Yilmaz et al. 2009 [19] | 15 years old female | Mandibular anterior region | No associated impacted teeth | Ameloblast like cells forming duct-like structures, eosinophilic droplets, and odontogenic calcifications | Periapical radiolucency with fine calcifications | Extrafollicular variant, with slow-growing and symptomless pattern |
| 21.   | Kothari et al. 2010 [16] | 25 years old female (second trimester of pregnancy) | Maxilla | Firm swelling | Cystic lining component of reduced enamel epithelium continuous with a more basaloid appearing lining epithelium, with microcystic adenomatoid odontogenic tumor mimicking a periapical cyst in a pregnant woman | Well-defined oval radiolucency, loss of lamina dura | |
| 22.   | Phillips et al. 2010 [17] | 16 years old male | maxilla | Swelling with the associated impacted tooth. | | Well-defined oval radiolucency | Features of ameloblastic fibro-odontoma, calcifying odontogenic cyst seen with AOT. |
| 23.   | Tejasvi et al. 2010 [18] | 15 years old male | Left maxillary incisor region | No associated impacted teeth | Odontogenic epithelium in duct-like pattern, eosinophilic coagulum | Well-defined unilocular radiolucency | Rare subvariant of the extrafollicular type of AOT mimicking periapical disease radiographically. AOT associated with a dentigerous cyst in the posterior maxilla. |
| 24.   | John et al. 2010 [12] | 39 years old female | Left maxillary premolar to molar region | Associated with impacted molar tooth | Whorls, rosettes, and duct-like pattern of epithelial cells with calcification | Well-defined unilocular radiolucency | |
| S. No. | Author/year | Age Gender | Site | Clinical features | Histopathological features | Special investigations | Concept proposed |
|--------|-------------|------------|------|------------------|---------------------------|------------------------|------------------|
| 25.    | Soares et al. 2011 [19] | 2 years old female | Maxilla | slow-growing swelling in the maxillary region | solid nodules, whorls, and rosettes pattern with eosinophilic material and areas of abortive enamel. Nests of ghost epithelial cells found in the lining of an ameloblastomatous epithelium. Pseudo-tubular structures, acidophilic hyaline-like material, dystrophic calcifications and a well-demarcated radiopaque border. | Large unilocular radiolucency with multiple radiopaque clusters and a well-demarcated radiopaque border immunohistochemically positive reaction for Bcl-2 and estrogen receptor. | Areas of CCOT with abortive enamel formation. AOT associated with CCOT termed as hybrid tumor. |
| 26.    | Sekia et al. 2011 [48] | 21 years old female | Right maxillary incisor to molar region | Associated with an impacted canine | solid nodules of columnar cells and spindle-shaped cells of odontogenic epithelium forming nests and rosette-like structures. Nests of ghost epithelial cells found in the lining of ameloblastomatous epithelium. Pseudo-tubular structures, acidophilic hyaline-like material, dystrophic calcifications and a well-demarcated radiopaque border. | Unilocular radiolucency, root resorption | AOT enlargement during pregnancy. |
| 27.    | Agarwal et al. 2012 [49] | 15 years old female | Maxilla | Non-tender expansion of the left maxilla with missing canine tooth | solid nodules of columnar cells and spindle-shaped cells of odontogenic epithelium forming nests and rosette-like structures. Nests of ghost epithelial cells found in the lining of ameloblastomatous epithelium. Pseudo-tubular structures, acidophilic hyaline-like material, dystrophic calcifications and a well-demarcated radiopaque border. | Unilocular radiolucency, root resorption | Tumor-associated with a dentigerous cyst in a pediatric patient. |
| 28.    | Laheji et al. 2012 [24] | 13 years old male | Mandibular left the anterior region | Associated with missing tooth | Dentinoid-like deposits a Follicular variety of AOT, mimicking as a dentigerous cyst. | Unilocular radiolucency, root resorption | Follicular variety of AOT, mimicking as a dentigerous cyst. |
| 29.    | Li et al. 2013 [50] | 22 years old | Swelling of the right maxilla | Associated with missing tooth | Cystic lesion surrounded by prominent fibro-osseous reaction corresponding to ossicles and cementicles. | Large unilocular radiolucency | AOT with solid portion showing calcified spherules characteristic of ossifying fibroma. |
| 30.    | Gomez et al. 2013 [51] | 32 years old male | left posterior mandible | expansion of the retromolar trigone | solid areas formed by dentin with lacunar borders lined by ameloblast-like cells with areas showing enamel matrix-like appearance odontogenic islands in the form of rosette-like structures. | Unilocularity of dense tumor. | AOT associated with odontoma. |
| 31.    | Prakasam et al. 2013 [25] | 19 years old female | Maxilla | Swelling and displacement of teeth | Columnar cells in the form of nests and rosette-like structures, with eosinophilic amorphous material "tumor droplets." Connective tissue showed clear cell changes. | Well-defined intrabony radiolucency with sclerotic margins. Diastase digestion PAS positive. Glycogen content done for clear cell change. | Clear cell change can be an indication of the process of cellular degeneration or its odontogenic epithelial origin. |
| 32.    | Mohanty et al. 2014 [17] | 20 years old female | Left maxilla | Buccal and palatal cortical plate expansion. | Columnar cells in the form of nests and rosette-like structures, with eosinophilic amorphous material "tumor droplets." Connective tissue showed clear cell changes. | Well-defined intrabony radiolucency with sclerotic margins. Diastase digestion PAS positive. Glycogen content done for clear cell change. | Clear cell change can be an indication of the process of cellular degeneration or its odontogenic epithelial origin. |
| 33.    | Rathod et al. 2014 [26] | 13 years old male | Mandible | Associated with an impacted tooth | Well-demarcated, unilocular radioluencies corresponding to that of a follicular (pericoronal) type of AOT. | Unilocular, well-demarcated radiolucency with a suggestive image of peripheral opaque bone condensation | AOT associated with odontoma. |
| 34.    | Bonardi et al. 2015 [27] | 7 years old female | Mandible | Associated with an impacted tooth | intraluminal proliferation of the epithelium, with polarized nuclei with rosette and spiral pattern and structures resembling ducts. Nests of ghost epithelial cells found in the lining of ameloblastomatous epithelium. Pseudo-tubular structures, acidophilic hyaline-like material, dystrophic calcifications and a well-demarcated radiopaque border. | Well-defined radiolucency with sclerotic rim. | Adenomatoid odontogenic tumor in a pediatric patient. |
| 35.    | Grover et al. 2015 [28] | 14 years old male | Left maxillary region | Fimbriated, non-tender swelling, associated with impacted maxillary canine | Cystic epithelium resembling reduced enamel epithelium, rosette-like structures about a central space containing eosinophilia material. | Well-defined radiolucency with sclerotic rim. | Suggested that all AOTs begin as a cyst derived from either REE or HERS. |
A molecular study by Razavi et al. showed that the Ki-67 labeling index was lower in AOTs as compared to SMAs, signifying a hamartomatic nature [58]. However, using a human androgen receptor gene polymorphism assay, Gomes et al. found that AOTs are monoclonal and, therefore, neoplastic [59]. Certain characters or features of AOT which suggest it to be true neoplasm or hamartoma as stated by various authors

Neoplasm

Small size and probable early detection and it’s removable before this slow-growing neoplasm reach considerable size [9]. Microscopical features show the greater difference from normal odontogenic apparatus than would have seen in a developmental anomaly [54]. It has been stated that many cases have gone undetected and untreated for many years due to their size and ultimately resulted in facial asymmetry and distortion. Using a human androgen receptor gene polymorphism assay, Gomes et al. found that AOTs are monoclonal and, therefore, neoplastic [60-63].

Hamartoma

In 2004, Rick stated that the limited size of AOT, its minimal growth potential, and the lack of recurrence even after incomplete removal attributed to its hamartomatic nature [6]. Low expression of BCL2 and Ki67 activity compared to ameloblastoma [58]. Medeiros et al. in 2005 conducted a study where they used proliferating cell nuclear antigen (marker for mitosis activity) and P53 (marker that indicates proliferative and anti-apoptotic activities) in AOT cases and found that IHC markers were very low thus they stated AOT as hamartoma rather than tumor [58,64].

Histogenesis of AOT

The origin of AOT is from the odontogenic epithelium; this fact is well established; however, the progenitor cell or tissue is not yet settled and still under discussion. The suggested cells by various authors are enamel organ [65,66], reduced enamel epithelium (REE) [67], undifferentiated odontogenic epithelium or stratum intermediate cells [68], stratum intermedium cells [69,70], and dental lamina and its remains [Philipsen and Reichart, 1999, Philipsen et al, 1992] [15].

Electron microscopic studies of duct-like structures formed within the tumor revealed the presence of hemidesmosomal junctions and evidence of basal lamina at the luminal pole of these cells. They also show secretory granules and coated vesicles near the luminal pole which are suggestive of a morphology similar to pre-ameloblasts. The eosinophilic material coexpressed basement membrane extracellular matrix proteins such as laminin, type IV collagen, heparin sulfate proteoglycan, fibronectin, and also enamel matrix proteins [71,72]. Furthermore, these cells are negative reactivity of these cells to lactoferrin and a1-antichymotrypsin anti-bodies which rule out glandular origin [14].

The non-duct-forming columnar cells expressed amelogenin reactivity, whereas the duct-forming cells showed no reactivity to amelogenin [71] or the other enamel matrix protein (enamelin and shatlin) antibodies [73-75]. The ultrastructural studies show that the small, irregular calcifications may be partially composed of atypical enamel is supported by its positive reactivity to amelogenin, enamelin, and enamelysin although it is indistinguishable from calcified amyloid [76].

The epithelial tumor cells display features that are consistent with neoplastic (pre)ameloblasts in a state of arrested development [77]. The ameloblasts are yet metabolically active enough to produce basement membrane and enamel matrix proteins [78]. It is theorized as a neoplastic growth of odontogenic epithelium. Glickman et al. drew an inference by saying that "such a controversy is irresolvable because sound arguments can be advanced in favor of and against both hypotheses. The arguments are based on personal bias rather than on scientific evidence" [8,57].
that the accumulation and subsequent degradation of these enamel secretory products by enzymes such as enamelysin are responsible for the development of the duct-like structures [71]. These structures are in fact enclosed spherical microcysts and their nature whether completely intraepithelial or stromal is debatable [79].

The tumor may be partly cystic, and in some cases, the solid lesion may be present only as masses in the wall of a large cyst. It is generally believed that the lesion is not a neoplasm [80,81].

Although the definition states that the lesion may have a cystic nature, very few case reports have described the cystic lining. Cystic presentation of AOT has been reported way back in 1915 by Harbitz who reported the lesion as “cystic adamantoma” [82].

Philipsen et al. have strongly argued in favor of the concept of AOT being derived from the complex system of the dental lamina or its remnants [11]. Marx and Stern considered AOT as a cyst and not a tumor and further gave a new terminology for this lesion, “adenomatoid odontogenic cyst (AOC).” Marx and Stern proposed that AOTs should not be considered tumors but cysts with a hamartomatous intraluminal proliferation of epithelial cells derived from the Hertwig’s epithelial root sheath (HERS) [9]. However, Rick stated that AOTs were benign embryonal neoplasms; he disagreed with the change in terminology as the majority of lesions have a predominantly solid component instead of a fluid-filled cavity. According to Marx and Stern, the AOT does not arise from the follicle of the tooth crown but instead arises from HERS, which would explain the finding of the tooth being completely within the lumen rather than the tooth root being within a bony crypt.

Considering all the case reports of AOT associated with dentigerous cyst, it is very much evident that the tumor is originating from the cystic lining. Moreover, the WHO definition of AOT given by Philipsen et al supports this fact of cystic lining to be the progenitor for tumor in many cases. Since the origin of the cystic lining in the dentigerous cyst is REE and not the dental lamina, we propose the former to be the progenitor of AOT.

IHC, it has been shown that the immunophenotypic profile of REE and AOT epithelium is virtually identical [83]. The expression of CK14 and the ultrastructural aspects of the AOT probably indicated its origin in the reduced dental epithelium [83]. Where CK14 showed expression in the cells which were between the spinelled and duct-like structures, these structures formed a cell group comparable to post-secretory ameloblasts of the REE, which was surrounded by a second group, composed of flat fusiform cells, which was similar to that of stellate reticulum. This justifies the expression in all epithelial cell elements of other AOTs and the REE, regardless of the histological characteristics [15]. Laminin was clearly present in the luminal surface of the adenomatoid structures and the lighter eosinophilic intercellular deposits, either focal or linear, which is compatible with the surface of the REE during the protective stage of amelogenesis. Nevertheless, the authors believed that some cells of AOT (cribriform areas) would resemble dental lamina (primitive cell), while others would represent histodifferentially more mature secretory phase of odontogenesis [15].

CONCLUSION

In classical AOT (solid), the proliferation of nodules originating from the cystic lining fills up the entire lumen whereas in cystic variant this process is incomplete and is thus seen only in parts of the cystic lining. Since the origin of the cystic lining is similar to a REE and not the dental lamina, we propose the former to be the progenitor of AOT. Furthermore, we consider extra-follicular, as well as peripheral AOTs, originate from the remnants of HERS (epithelial rests of Malassez), which comply with the common histology for all these variants [28].

AUTHOR’S CONTRIBUTION

Sahana P Ahmed: Compiled full literature search and drafted the manuscript. Arulmozhi Nandakumar: Developed the standards of manuscript. Ramya Ramadas: Supervised the manuscript making, and edited the manuscript. Karunya Krishnakumar: Provided guidance in the preparation of the manuscript.

CONFLICTS OF INTEREST

Authors declare that they have no conflicts of interest.

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