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Metal Ions Complexes and Viral Pathogenicity

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Abstract

Metal ions form the integral part of some viral proteins and as play an important role in their survival and pathogenesis of the virus. Prominent metal ions that bind with virus proteins include magnesium, zinc and copper. Metal ions participate in maturation of genomic RNA in viruses, activation and catalytic mechanisms, reverse transcription, initial integration process and protection of newly synthesized DNA, inhibition of proton translocation (M2 protein), minus-and plus-strand transfer, enhance nucleic acid annealing, activation of transcription, integration of viral DNA into specific sites and act as a chaperone of nucleic acid. The structural proteins of viruses protect the viral genome, participate in attachment of virus to a susceptible cell, facilitate transfer of viral nucleic acid from one host cell to another and are antigenic determinants of the virus. The involvement of metal ions in the structure of common protein metal finger gives the metal a particular position in the reaction. The cellular system control metal ions balancing in constituting a natural protective barrier that limits the accessibility of metal ions and thus interferes with viral replication.

Keyword: Viral protein, Virus, Nucleoprotein, Metal, Metalloprotein, Zinc.

Introduction

Metal ions play an important roles in biological processes which include bridging the distant residues or domains of proteins, mediate interactions between proteins and ligands, serve in the active site as a nucleophilic catalyst and also in transfer of electron (Tiraboschi *et al.,* 218).

Most biological processes are mainly metal ion specific, although more than one metal ion can play each of these roles. For example, the coagulation cascade is Calcium ion (Ca^{2+}) specific, protein biosynthesis is primarily magnesium ion (Mg^{2+}) specific, several enzymes are zinc ion (Zn^{2+}) ion specific and the oxidative processes are often iron ion (Fe^{2+}/Fe^{3+}) (Tiraboschi *et al.,* 2018). The conformational changes induced by binding a metal ion are

remarkable. Residue side chains, which are greater are part in the metal ion-free structure, may become constituents of the metal ion-binding site (Deerfield *et al.,* 2019).

A number of trace metals are essential micronutrients in human body and their deficiency that cause infectious diseases often coexist and exhibit complex interactions in the system of human. Several trace metals such as zinc, copper and manganese, etc. influences the susceptibility to; the course and the outcome of a variety of viral infections. Deficiency of such trace metals is known to alter the genome of the viruses and the grave consequences of this may be the emergence of new infections (Chaturvedi *et al.,* 2020).

On the other hand, some metals like hexavalent chromium may have toxic effects on the immune system of human being (Shrivastava *et al.,* 2018). Metals are integral part of several viruses (Shrivastava *et al.,* 2019) and are known to play important role in their survival and pathogenesis.

Literature Review

Gandhi *et al.,* 2018 reported that binding of Cu^{2+} to the high affinity site results in an approximately equal inhibition of both inward and outward currents. The wild-type protein has very high specificity for Cu^{2+} and is only partially inhibited by nickel (Ni^{2+}), platinum (Pt^{2+}), and Zn^{2+}.

Aartjan *et al.,* 2020 reported that chelating Zn^{2+} with MgEDTA, the inhibitory effect of the divalent cation could be reversed which provides a novel experimental tool for in vitro studies of the molecular details of coronavirus replication and transcription.

Teoh*et al.,* 2018 reported that Shope fibroma virus SOD retains the zinc binding properties of its cellular homolog, but cannot bind copper. Further, recombinant Shope fibroma virus SOD forms very stable complexes with cellular copper chaperones for SOD.

Degenkolbe *et al.,* 2018 reported that the E6 protein of HPV 16 has two putative Zn^{2+} binding sites crucial for its function. A specific chelating agent, which functionally mimics a metallochaperone, stabilizes the soluble monomeric form of E6 and inhibits multimerization*in vitro*.

Pfister *et al.,* 2020 reported that cysteine-rich motif is sufficient to bind zinc when undergo *in vitro* but not less potent to bind *in vivo*. The metal binding site is also conserved in the chymotrypsin-like 2A cysteine proteinases of picornaviruses.

Stempniak *et al.,* 2018 explained that potentionmetric and spectroscopic data have shown that a fragment of envelope proteins of the hepatitis B virus could be a very specific binding molecule for Cu^{2+} ions using arginine lateral NH_2 donor sites. The presence of Pro and Asp residues makes Arg binding not only very specific, but also very efficient.

Yoo, *et al.,* 2020 reported that the binds of metal ions with viral proteins have a greater transcription or viral replication and its structure unusual have heterotricyclic compounds which serve several roles in the binding, this include Zn^{2+}chelator, and a target of interest is HIV-1 ZF, HIV-1 RNA-binding NC7. In addition, the targets of BN could be via adsorption, transcription and/ or viral RNA replication of interestingly wide range RNA viruses.

Composition of Viron

Viruses are the smallest infectious agents containing only one type of nucleic acid (Deoxyribonucleic acid or Ribonucleic acid) covered by a protein coat, which may be surrounded by a lipid-containing membrane. A virion is composed of viral proteins, nucleic acid and, lipids and carbohydrates. A viral protein is both a component and a protein of a virus. Viral proteins are grouped according to their functions, and groups of viral proteins include structural proteins, non-structural proteins, regulatory and accessory proteins (Yoon and Walterhouse, 2020).

The structural proteins of viruses protect the viral genome, participate in attachment of virus to a susceptible cell, facilitate transfer of viral nucleic acid from one host cell to another and are antigenic determinants of the virus (Knipe and Howley, 2018).

Viral envelopes contain lipids and glycoproteins (gp), the lipids are derived from the host cell while the glycoproteins are virus-encoded, while surface glycoproteins attach the virus to a target cell and are important viral antigens. Viral proteins coded by nonstructural genes are known as nonstructural proteins (NS) (Knipe and Howley, 2018).

Present in the virus-infected cells, these proteins appear to have regulatory roles during replication. For instance, the hepatitis C virus (HCV) genes code for NS2, NS3, NS4A, NS4B, NS5A, and NS5B nonstructural proteins (Knipe and Howley, 2018). The mature structural proteins are C, E1 and E2(Yoon and Walterhouse, 2020).

Protein-Metal Interactions

An interaction between a protein and a metal ion is of different types. Metalloprotein is a generic term for a protein that also contains a metal cofactor. One-third of all proteins are ‘‘metalloproteins’’. The metal ions in metalloproteins are critical to the proteins function, structure, or stability and numerous essential biological functions (Dudev and Lim, 2019).

Understanding and ultimately controlling the binding and activity of protein metal sites are of immense biological and medical importance. The functions of metalloproteins having metals that bind with different viral proteins are presented in Table 1 (Chaturvedi *et al.,* 2020).

Table 1 end of the paper

Three proteins have been identified in mammals: GLABROUS1 (GLI), GLI2, and GLI3, they are highly conserved in zinc finger (ZF) domain and function as transcription factors in the vertebrate sonic hedgehog patched signaling pathway (Yoon and Walterhouse, 2020).

During evolution some proteins allegedly have chosen Mg^{2+} as a natural cofactor. Mg binding sites appear to be weak and can be replaced by other divalent metals like Zn^{2+} and in some cases, inhibit enzymatic activity. Therefore, it seems that the cell machinery governs the process of metal binding by regulating appropriate concentrations of Mg^{2+} and Zn^{2+}etc (Dudev and Lim, 2019), in various biological compartments.

Zn^{2+} has a higher affinity for a protein ligand and strongly prefers a tetrahedral geometry. Consequently, rigid Zn^{2+}-binding sites appear to be more selective than Mg^{2+}-binding sites, and a protein can generally select Zn^{2+} against the background of a much higher Mg^{2+} concentration (Dudev and Lim, 2019).

Among the metal, zinc is most often known to binding viral protein. Zinc is the second most abundant trace metal found in eukaryotic organisms, second only to iron. Zinc is required for essential catalytic functions in more than 300 enzymes, stabilization and induction of the folding of protein sub domains. The latter functions include the essential role of zinc in the folding of the DNA-binding domains of eukaryotic transcription factors, including the ZF transcription factors (Coleman, 2019).

ZF are small protein domains in which zinc plays a structural role contributing to the stability of the domain and are small DNA-binding peptide motifs. The cysteine-rich zinc-binding motifs known as the RING and B-box are found in several unrelated proteins(Coleman, 2019; Krishna *et al.,* 2018).

ZF are structurally diverse a when they complex with the viral proteins to perform a broad range of functions in various cellular processes, such as replication and repair, transcription and translation, metabolism and signaling, cell proliferation and apoptosis. ZF typically function as interaction modules and bind to a wide variety of compounds, such as nucleic acids, proteins and small molecules. Three of these fold groups comprise the majority of ZFs, namely, C_2H_2-like finger, treble clef finger and the zinc ribbon(Krishna *et al.,* 2018).

The binds of metal ions with viral proteins have a greater transcription or viral replication. The structurally unusual heterotricyclic compounds haveseveral roles in the binding which include Zn^{2+}chelator, and a target of interest is HIV-1 ZF, HIV-1 RNA-binding NC7. In addition, the targets of BN could be via adsorption, transcription and/ or viral RNA replication of interestingly wide range RNA viruses (Yoo, *et al.,* 2020).

Metal Ion Interaction with Corona Viruses

The NS polypeptide is encoded by the ORF1b of human corona virus 229E (HCoV-229E) is a zinc-binding protein (Yoo *et al.,* 2020). HcoV-229E papain-like proteinase and its corona

viral relatives have a poorly conserved ZF connecting the left and right hand domains of a papain-like fold.

In denaturation/ renaturation experiments using the recombinant protein (Herold *et al.,* 2019), its activity is strongly dependent upon Zn^{2+}. The 229E replicate gene encodes a protein, p66HEL, which contains a putative ZF structure linked to a putative super family, is helicase (Seybert *et al.,* 2018).

It also encodes NS13 containing an N-terminal zinc-binding domain and a C-terminal super family 1 helicase domain (Ivanov and Ziebuhr, 2018). Corona virus replication and transcription are highly specialized processes of cytoplasmic RNA synthesis that localize to virus-induced membrane structures.

The enzymatic activities of a recombinant form of the severe acute respiratory syndrome corona virus (SARS-CoV) helicase NS13; a super family is helicase with an N-terminal zinc-binding domain has been characterized. NS13 has both RNA and DNA duplex unwinding activities (Ivanov *et al.,* 2018).

Increasing the intracellular Zn^{2+} concentration with zinc ionophore like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses, including Corona viruses. The coronavirus effect has corona viruses (Aartjan*et al.,* 2020).

Enzyme attributed to interference with the viral polyprotein processing. The combination of Zn^{2+} and PT at low concentrations inhibits the replication of SARS-coronavirus (SARS-Cov) and equine arteritis virus (EAV) in cell culture. The RNA synthesis of these two distantly related nidoviruses is catalyzed by an RNA dependent RNA polymerase (RdRp), which is the core enzyme of their multiprotein replication and transcription complex (RTC). Using an activity assay for RTCs isolated from the cells infected with coronaviruses thus eliminated the need for PT to transport Zn^{2+} across the plasma membrane which shows that Zn^{2+} efficiently inhibits the RNA synthesizing activity of the RTCs of corona viruses (Aartjan*et al.,* 2020).

Enzymatic studies using recombinant RdRps (SARS-CoV) purified from *E. Coli* subsequently revealed that Zn^{2+} directly inhibited the *in vitro* activity of coronavirus polymerase. More specifically, Zn^{2+} was found to block the initiation step of CoV-RNA synthesis, whereas in the case of the SARS-CoVRdRp elongation was inhibited and template binding reduced (Aartjan *et al.,* 2020).

Metal Ions Interactions in Papilloma Viruses and Ebola Virus

The purified oncogenic E7 proteins of human papilloma virus (HPV 16) and of cottontail rabbit papilloma virus (CRPV) contain one tightly bound Zn^{2+} per molecule. The metal site shows facile exchange with either cadmium (Cd^{2+}) or Cu^{1+}. The HPV 16 E7 maximally binds

one Cd^{2+} or two Cu^{1+} ions, while the CRPV E7 binds two Cd^{2+} or three Cu^{2+} ions(Roth *et al.,* 2019).

The E6 protein of HPV 16 has two putative Zn^{2+} binding sites crucial for its function. A specific chelating agent, which functionally mimics a metallochaperone, stabilizes the soluble monomeric form of E6 and inhibits multimerization *in vitro*(Degenkolbe *et al.,*2018).

It is presumed that chelating agents of appropriate strength could assist zinc delivery to recombinant metalloproteins in vitro and may even destabilize existing agglomerates. *VP30, VP35, VP40 and GP*isessential activator of Ebola virus transcription (Modrof *et al.,* 2019). A conspicuous structural feature of VP30 is an unconventional zinc-binding Cys(3)-His motif that stoichiometrically binds Zn^{2+} in a one-to-one relationship. Substitution of the conserved cysteines and histidine within the motif leads to a complete loss of the capacity for zinc binding (Modrof *et al.,* 2019).

Metal Ions Interaction in Picorna and Rhinoviruses

Metal ions interact with picorna and rhinoviruses through Protein 2C (ATPase) of picornaviruses is involved in the rearrangement of host cell organelles, viral RNA replication, and encapsidation. The cysteine-rich motif near the carboxyl terminus of poliovirus 2C (ATPase) is well conserved among enteroviruses and rhinoviruses displaying an amino acid arrangement resembling ZF motifs (Pfister*et al.,* 2020). A mutant virus that lacks the second of four potential coordination sites for zinc is temperature sensitive.

The cysteine-rich motif is sufficient to bind zinc when undergo *in vitro* but not less potent to bind *invivo*. The metal binding site is also conserved in the chymotrypsin-like 2A cysteine proteinases of picornaviruses (Pfister*et al.,* 2020).

The zinc atom is not directly involved in catalysis but rather may have a structural role. The coordination of the structural zinc in the HCV NS3 proteinase is mediated by Cys-97, Cys-99, Cys-145, and His-149. A similar metal binding motif is found in 2A proteinases of enteroviruses and rhinoviruses, suggesting that they are structurally related (Stempniak*et al.,* 2018).

Metal Ions Interaction in Poxviruses

Poxviruses (member of the poxviridae family) can infect both humans and animals. The orthopoxviruses include small pox (variola, monkey pox and vaccina. Vaccination with vaccinia virus has been directly responsible for the success eradication of smallpox (variola) which is the family of poxvirus.

Almazan *et al.,* 2019 reported that the open reading frame of the A45R gene from vaccinia virus (VV) strain encodes a 125-amino-acid protein with 39% amino acid identity to copper-zinc superoxide dismutase (Cu-Zn SOD).

The sequence of the A45R gene from other orthopox viruses shows that the protein that bind with the viruses are highly conserved in all viruses sequenced, including 16 strains of VV, 2 strains of cowpox virus, camelpox virus, and 4 strains of variola virus(Almazan *et al.,* 2019)

In all cases the protein lacks key residues involved in metal ion binding that are important for the catalytic activity. A45R is reported neither virus replication nor virulence. *Molluscumcontagiosum*, a DNA virus, has been shown to encode a functional selenium-dependent GPx enzyme(Zhang *et al.,* 2018).

Many Chordopoxvirusesusually encode catalytically inactive homologs of cellular Cu-Zn SOD. The biological function of these proteins is unknown, although the proteins that bind by encoding with Leporipoxviruses have been shown to promote a slow decline in the level of SOD activity in virus-infected cells (Almazan*et al.,*2019).

Teoh*et al.,* 2018reported that Shope fibroma virus SOD retains the zinc binding properties of its cellular homolog, but cannot bind copper. Further, recombinant Shope fibroma virus SOD forms very stable complexes with cellular copper chaperones for SOD.

Similar viral SOD/chaperone complexes are formed in cells infected with a closely related myxoma virus. These poxviral SOD homologs do not form stable complexes with cellular Cu, Zn-SOD or affect its concentration (Teoh *et al.,* 2018).

Metal Ions Interactions in Hepatitis Viruses

The NS3 region of the hepatitis C virus (HCV) encodes for a serine protease activity, which is necessary for the processing of the nonstructural region of the viral polyprotein. The minimal domain with proteolytic activity resides in the N terminus, where a structural tetradentate zinc-binding site is located. The zinc-binding site has a role in maintaining the structural stability and guiding the folding of the NS3 serine proteinase domain(De Francesco *et al.,* 2018).

The ligands that bind with the metal have been identified by X-ray crystallography as three cysteines and one histidine residue, postulated to coordinate the metal through a water molecule. The structure of NS3 proteinase from HCV BK strain has a substrate-binding site consistent with the cleavage specificity of the enzyme. Novel features include a structural zinc-binding site and a long N-terminus that interacts with neighboring molecules by binding to a hydrophobic surface patch (Love *et al.,* 2020).

Evidence for rearrangements of the metal coordination geometry induced by complex formation with an NS4A peptide cofactor has been reported (Urbani*et al.,* 2018). The HCV NS3 protein N-terminal domain has a zinc-binding site exposed on the surface(Love *et al.,* 2020).

The HCV enzyme contains Zn^{2+} with NS3 ligation and that the metal is required for structural integrity and activity of the enzyme. HCV polyprotein processing is activated by Zn^{2+} and, to a lesser degree, by Cd^{2+}, Pb^{2+}, and Co^{2+} and is inhibited by Cu^{2+} and Hg^{2+} ions (Barbato *et al.,* 2019).

Zn^{2+} is not directly involved in catalysis but may have a structural role (Stempniak *et al.,* 2018). The three cysteines and the histidines coordinate the structural role of zinc in the HCV NS3 proteinase at a Zn^{2+}binding site while dengue 2 virus NS3 protease, though lot of homology, does not contain a Zn^{2+}binding site(Brinkworth *et al.,* 2019). Zn^{2+}depend on HCV NS3 inhibition is relatively insensitive to the structural variations but dependent on the presence of negatively charged functionality (Yeung *et al.,* 2020).

This can be interpreted in the context of an initial electrostatic interaction between protease and inhibitor that is subsequently consolidated by Zn^{2+}, with binding facilitated by the featureless active site and proximal regions of the HCV NS3 protein. NS5A gene product displays a multitude of activities related to enhancement of viral pathogenesis. A complex multimechanistic role of NS5A in promoting viral persistence, pathogenesis and, indirectly, viral-related hepatocarcinogenesis indicates its key role in HCV pathobiology (Barbato *et al.,* 2019; Yeung *et al.,* 2020).

Potentionmetric and spectroscopic data have shown that a fragment of envelope proteins of the hepatitis B virus could be a very specific binding molecule for Cu^{2+} ions using arginine lateral NH_2 donor sites. The presence of Pro and Asp residues makes Arg binding not only very specific, but also very efficient (Stempniak *et al.,* 2018).

Metal Ions Interactions in Influenza Virus

The homotetrameric M2 membrane protein of influenza virus forms a proton-selective ion channel by biding with metal. Cu^{2+} strongly and reversibly inhibits membrane currents with biphasic reaction kinetics (Gandhi *et al.,* 2018).

Binding of Cu^{2+} to the high affinity site results in an approximately equal inhibition of both inward and outward currents (Gandhi *et al.,* 2018). The wild-type protein has very high specificity for Cu^{2+} and is only partially inhibited by nickel (Ni^{2+}), platinum (Pt^{2+}), and Zn^{2+} (Gandhi *et al.,* 2018).

The M1 protein has a peptide linker (M1Lnk). The pH-dependent conformational transition of M1Lnk strongly suggests that the inter domain linker region of M1 also undergoes a pH-dependent unfolding-refolding transition in the presence of Zn^{2+}. A small but significant portion of the M1 protein is bound to Zn^{2+} in the virion. The Zn2+-bound M1 molecule may play a special role in virus uncoating by changing the disposition of the N- and C-terminal domains upon acidification of the virion interior(Okada *et al.,* 2019).

The influenza virus RNA-dependent RNA polymerase protein complex contains an associated RNA endonuclease activity, which is dependent on the presence of divalent metal ions. Virus-specific RNA cleavage by endonuclease is observed with various metal ions, and maximum cleavage activity is obtained with Mn^{2+} or Co^{2+} and is much less with Mg^{2+} (Okada *et al.,* 2019).

Synergistic activation of cleavage activity is observed with combinations of different metal ions at varying concentrations. These results support a two-metal ion mechanism of RNA cleavage for the influenza virus cap-dependent endonuclease.

A peptide containing the CCHH motif binds to zinc in a one-to-one complex reaction with the characteristics of a typical zinc-binding peptide to form a strain tha will influence the transcription and inhibition of the proteins (Yoo *et al.,* 2020). Intact influenza virus also contains zinc bound to the M1 protein, but the amount varies in different strains. The zinc content has no influence on the RNA binding and transcription inhibition activities of various M1 proteins (Elster *et al.,* 2019).

The foregoing suggests that the zinc in M1 has a structural role in the virion other than nucleic acid binding. A peptide synthesized to the ZF region of the M1 sequence of influenza virus strain is effective as a polymerase inhibitor. This peptide represents a ZF and has antiviral activity (Herold *et al.,* 2018).

Reduction in the number of residues involved in coordination of Zn^{2+} abolishes antiviral activity. In addition, this protein has antiviral activity against other type A influenza viruses (H1N1, H2N2, and H3N2 subtypes), influenza B and vesicular stomatitis viruses(Nasser *et al*., 2019).

Metal Selectivity of Viral Protein

Viral proteins are known to have affinity for specific metal ion (Chruscinski*et al.,* 2019). The factors that define the energetically most favorable ligand coordination set and geometry for a given metal cation are ill defined. For instance, the selectivity of viral protein to a specific metal cation from mixture pool of ions in the surrounding fluids is unclear. Likewise, the preference of viral proteins and nucleoproteins primarily to zinc ions defies clarity? It is speculated that the metal selectivity of viral protein could be due to:

(i) The natural abundance of the metal in the biological locality, or
(ii) Nature of the metal (e.g., its stereochemical and charge to size ratio), or
(iii) Nature of the protein (e.g., its unique set of amino acid residues forming the metal-binding pocket and the stereochemistry of this pocket) (Coleman, 2019)?

Conclusion

The review concluded on the several ways on how metal ions interact with viral protein, binding and transcription to render the viral pathogen inactive**.** The review is done in order to understand the deeper interaction and structural basis of metal binding with viral protein and how it is important in design and development of viral inhibitors that may eventually lead to new drug discovery**.**

The review explain the molecular mechanism controlling cellular metal that enabled it ton undergo mechanistic studies on the functions of protein encoded. The integration of all the interactions leads to discovery of host-virus interaction, showing that the mechanism controlling cellular metal ions trafficking constitute natural antiviral barrier. This interactions describes the role of metal ions as a cofactor of viral proteins, suggest that the accessibility of metal ions in infected cells could be a potentially limiting factor in the virus life cycle.

This review underscores the importance of metal ions in the survival and pathogenesis of large group of viruses. It also gives insights to the structural basis whilst emphasizing their role on metal binding design and development of viral inhibitors. The viral protein interaction with metals ions is a needful review that shows interaction of various metals with different viral proteins as such efforts is akin to the advancement of the study of new antiviral agents.

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Table 1.Functions of Some Metals in Metallo-Proteins Interactions

S/N	Metals	Enzyme and Protein Classes	Function	Examples
1	Zinc	Transferases, hydrolases, lyases, isomerases, ligases, oxidoreductases, transcription factor	They are enzymes that facilitate the transfer of specific functional groups from one molecule called donor to another called receptor reaction in the cell.	RNA polymerases, alcohol dehydrogenases, glucocorticoid receptor (De Francesco *et al.,* 2019).
2	Copper	Oxidoreductases	These enzymes function as the catalyzes that aid the transfer of electron from one molecule, the reductant, also called the electron donor, to another called oxidant also known as the electron acceptor	Superoxide dismutase, ferroxidase (ceruloplasmin) (Chaturvedi *et al.,* 2020).
3	Iron	Oxidoreductases	They are enzymes function as the catalyzes that aid the transfer of electron from one molecule, the reductant, also called the electron donor, to another called oxidant also known as the electron acceptor.	Cytochrome oxodase (Herold *et al.,* 2018).
4	Cobalt	Transferases	These enzymes assist in transfer of specific functional groups from one molecule called donor to another called receptor reaction in the cell.	Haemocysteine methyl-transferases (Brinkworth *et al.,* 2019).
5	Magnesium	Oxidoreductases, methyltransferase.	These are enzymes that function as the catalyzes that aid the transfer of electron from one molecule, the redundant, also called the electron donor, to another called oxidant also known as the electron acceptor.	Superoxide dismutase, protoporphyrin (Dudev and Lim, 2019).
6	Nickel	Oxidoreductases	These enzymes function as the catalyzes that aid the transfer of electron from one molecule, the redundant, also called the electron donor, to another called oxidant also known as the electron acceptor.	Hydrolases Urease (Chaturvedi *et al.,* 2020).

