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Review

Mechanisms of CO_2 reduction in bacteria based on molecular studies of formate dehydrogenase (FDH) enzymes

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ABSTRACT

Formate dehydrogenase (FDHs) is an enzyme that catalyzes the oxidation of formate ($HCOO^-$) to carbon dioxide (CO_2) and water, with the concomitant reduction of a cofactor such as NAD^+ (nicotinamide adenine dinucleotide) or $NADP^+$ (flavin adenine dinucleotide). This process produces energy, which cells can then employ for various metabolic functions. FDHs are key metabolic enzymes that perform critical roles in energy production, carbon dioxide fixation, and nitrogen metabolism in many bacterial species. FDH is a D-specific 2-hydroxy acid dehydrogenase found mostly in prokaryotes and eukaryotes. It is essential for the energy supply of methyl tropic organisms through hydride ion transfer and bio-transformations. Most metal-binding FDH enzymes, such as molybdenum and tungsten-containing enzymes, catalyze the redox process and oxidation of formate and serve as flexible biocatalysts for NADPH regeneration and consumption. Formate dehydrogenase is also utilized in biotechnology and biochemistry as a technique. It is extensively employed as an electron acceptor in enzymatic tests to create hydrogen gas via proton reduction. Furthermore, formate dehydrogenase has been researched for its potential application in the production of biofuels and other bioproducts. The current reviews emphasize the structural and functional characteristics of FDH and the primary mechanisms involved in FDH development. It examines the function of metal ions in FDH as well as its catalytic mechanism and characteristics.

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1. Introduction

Ecosystems and the environment are very worried about the increasing levels of carbon dioxide (CO_2) in the atmosphere. Carbon dioxide (CO_2) is a greenhouse gas that contributes to the warming of the Earth's atmosphere. Reducing atmospheric CO_2 levels has received much attention as an approach to combat global warming and address the shortage of fossil fuels. The abundance of CO_2 in the atmosphere has made it an exciting source for the production of fuels (Hossain and Puteh 2013). This process is known as carbon capture and utilization (CCU), which involves capturing CO_2 emissions from industrial processes or the atmosphere and using them as feedstocks to produce fuels, chemicals, and other products. The chemical conversion of CO_2 remains challenging because the mechanism of CO_2 reduction occurs through complicated steps and has high activation barriers, which makes the process energy-intensive(Vitillo et al., 2022). CO_2 is a very stable molecule, and breaking the strong carbon–oxygen bond requires significant energy. An effective strategy for lowering CO_2 in the air, carbon capture, sequestration, and utilization (CCSU) has gained widespread attention in recent years. CCSU involves capturing CO_2 emissions from industrial processes or the atmosphere, storing them in underground geological formations or other secure storage locations, and using them as feedstocks for the production of fuels, chemicals, and other products (Kumar et al., 2022).

The process of carbon capture entails collecting CO_2 emissions from sources like power plants and factories, then transporting and storing the gas in safe geological formations or other storage locations. The utilization of CO_2 into useful chemicals, materials, or fuels is an important area of research and development, as it can potentially reduce greenhouse gas emissions while also providing a source of sustainable products. However, a combination of CO_2 capture, sequestration, and utilization approaches can help reduce atmospheric CO_2 levels and mitigate the impacts of climate change (Wilberforce et al., 2021). However, these approaches still face technical and economic challenges that must be overcome to become widely implemented on a large scale. Photochemical and electrochemical CO_2 reduction are promising approaches for converting CO_2 into useful products, such as CO and formate. These processes involve using light energy or electrical energy to drive the reduction of CO_2. In photochemical CO_2 reduction, light energy excites electrons in a photosensitizer material, which then transfers to a catalyst that reduces CO_2 into CO or formate (De Luna et al., 2019).

The photosensitizer and catalyst can be separated or combined into a single material. The process can be optimized by selecting the right photosensitizer and catalyst materials and optimizing the reaction conditions. In electrochemical CO_2 reduction, an electrical potential is applied to an electrode in contact with a CO_2 solution to drive the reduction of CO_2 into CO or formate. This process requires a catalyst material to facilitate the reaction, which can be optimized to improve the efficiency and selectivity of the process. Both photochemical and electrochemical CO_2 reduction has the potential to be used as a means of converting CO_2 into valuable chemicals, such as CO and formate, which can be used as feedstocks for the production of fuels and other chemicals (Xu et al., 2022). However, these processes are still in the early stages of development and face technical and economic challenges that must be overcome to become viable solutions for reducing atmospheric CO_2 levels. Apart from this, recently, biological fixation of CO_2 and enzymatic CO_2 reduction are promising approaches for producing valuable chemicals such as formic acid, methanol, and ethanol. These processes involve using microorganisms and enzymes to convert CO_2 into useful products (Appel et al., 2013).

Biological fixation of CO_2 involves using microorganisms such as bacteria, algae, and plants to capture and convert CO_2 into organic compounds through photosynthesis. These organic compounds can then be used as feedstocks for producing chemicals such as formic acid, methanol, and ethanol. Enzymatic CO_2 reduction involves using enzymes to catalyze the conversion of CO_2 into valuable products such as formic acid, methanol, and ethanol (Biswas et al., 2011). This process can be optimized by selecting the right enzyme and optimizing the reaction conditions. Both biological fixation of CO_2 and enzymatic CO_2 reduction has the potential to be used as a means of converting CO_2 into valuable chemicals. However, these processes are still in the early stages of development and face technical and economic challenges that must be overcome to become viable solutions for reducing atmospheric CO_2 levels and producing sustainable products (Velty and Corma 2023). The vast majority of autotrophic organisms use CO_2 as their primary carbon source, and they have adapted numerous mechanisms to circumvent the energy costs of fixing CO_2. For this reason, CO_2 can be reduced to organic compounds via a number of different metabolic pathways.

One of the most well-known pathways for CO_2 fixation is the Calvin cycle, which is used by photosynthetic organisms such as plants and algae. The Calvin cycle is a cyclic pathway that involves the fixation of CO_2 into organic compounds such as sugars, using energy from ATP and NADPH produced during photosynthesis (Sharkey 2019). Another pathway for CO_2 fixation is the reverse TCA (tricarboxylic acid) cycle, which some bacteria and archaea use. The reverse TCA cycle involves the reduction of CO_2 to form organic acids such as succinate and malate, which can then be used as precursors for the biosynthesis of other compounds. Other pathways for CO_2 fixation include the 3-hydroxypropionate cycle, the 3-hydroxypropionate/4-hydroxybutyrate cycle, and the reductive acetyl-CoA pathway, which are used by certain bacteria and archaea (Huber et al., 2008). These pathways involve the reduction of CO_2 to form organic compounds such as acetyl-CoA, which can then be used as precursors for the biosynthesis of other compounds. Naturally, cells can adopt several routes for CO_2 metabolic processes. The six significant routes for CO_2 metabolism include the (i) Calvin cycle: This pathway is used by photosynthetic organisms such as plants, algae, and cyanobacteria to fix CO_2 and produce organic compounds such as glucose. (ii) Reductive citric acid cycle: This pathway is used by some bacteria and archaea to convert CO_2 into organic compounds such as acetyl-CoA and succinate. (iii) Reductive acetyl-CoA cycle: Some bacteria and archaea use this pathway to transform carbon dioxide into acetyl-CoA, which can then be used in biosynthesis. (iv) 3-hydroxypropionate cycle: This pathway is used by some bacteria and archaea to convert CO_2 into acetyl-CoA and other organic compounds. (v) Dicarboxylate/4-hydroxybutyrate cycle: This pathway

is used by some bacteria to convert CO_2 into organic acids such as succinate and 4-hydroxybutyrate. (vi) Methanogenesis pathway: This pathway is used by some archaea to convert CO2 into methane gas (Jayakumar et al., 2023). Notably, the dehydrogenases enzymes can transfer two hydrogen atoms (2H) from a reduced substrate to an electron acceptor. The transfer of these hydrogen atoms involves the substrate's oxidation and the electron acceptor's reduction. This process is a crucial step in many metabolic pathways, as it generates energy and allows for the synthesis of essential molecules such as ATP (adenosine triphosphate) and NADPH (nicotinamide adenine dinucleotide phosphate). Three different dehydrogenase enzymes are required to transform CO_2 into methanol: formate dehydrogenase (FDH), formaldehyde dehydrogenase (FLDH), and alcohol dehydrogenase (ALDH). In addition, NADH functions as a coenzyme during this electron transfer, with one NADH molecule being irreversibly oxidized to NAD^+ at each reduction step (Gruez et al., 2004).

1.1. Formate dehydrogenase (FDH)

Formate dehydrogenase is an enzyme that can catalyze the reduction of CO_2 to formate in certain microorganisms. The reaction involves the transfer of two electrons and two protons from a reduced cofactor, such as NADH or NADPH, to CO_2, which is then reduced to formate (Schlager et al., 2017). Formate dehydrogenase (FDH) is a stable enzyme, but hydrophobic interfaces can inactivate it. This is because FDH has a hydrophobic binding site sensitive to environmental changes, such as exposure to hydrophobic surfaces. The oxidoreductive interconversion of carbon dioxide and formic acid is catalyzed by FDH, a member of the D-specific 2-hydroxy acid dehydrogenase superfamily consisting of single subunits with four distinct domains. In many bacteria and eukaryotes, FDHs catalyze the final step of the catabolic process in which formate is oxidized to CO_2 (Deng et al., 2023). However, a certain type of FDH can also act as CO_2 reductase. Some redox enzymes also effectively catalyze reactions reversibly such as DMSO-reductase, succinate: quinine reductase, CO dehydrogenase, fumarate, menaquinone oxidoreductase, and some hydrogenases (Unden and Bongaerts 1997).

1.2. Type of formate dehydrogenase

Formate dehydrogenase (FDH) is a diverse family of enzymes found in various organisms, including bacteria, archaea, and eukaryotes. Several types of FDH enzymes differ in their structures, cofactor requirements, and catalytic activities. NAD-dependent FDH enzymes require the cofactor NAD^+ or $NADP^+$ for their activity, and are typically found in bacteria and some eukaryotes (Nielsen et al., 2019). They catalyze the interconversion of formate and CO_2 through an oxidoreductive process. Cytochrome *c*-dependent FDH enzymes require cytochrome *c* as a cofactor, and are found in certain bacteria and archaea (Makela et al., 2010). They are involved in the electron transport chain and play a role in the metabolism of various organic compounds. Molybdenum-dependent FDH enzymes require molybdenum as a cofactor, and are found in bacteria, archaea, and some eukaryotes. They are involved in the catabolism of various compounds, including formate, formaldehyde, and methanol. Tungsten-dependent FDH enzymes require tungsten as a cofactor, and are found in certain bacteria and archaea (Maia et al., 2015). They are involved in the catabolism of formate and other compounds and can also catalyze the reduction of CO_2 to formate. Iron-dependent FDH enzymes require iron as a cofactor and are found in some bacteria and archaea. They are involved in the catabolism of various compounds, and can catalyze the reduction of CO_2 to formate (Cotton et al., 2020).

1.3. Formate dehydrogenase – Metal-based classification

FDHs can be classified into two broad categories based on their cofactor requirements: metal-independent FDHs and metal-containing FDHs. Metal-independent FDHs enzymes do not require any metal cofactors for their activity. Instead, they utilize organic cofactors such as pyrroloquinoline quinone (PQQ) or flavin adenine dinucleotide (FAD) to transfer electrons during the catalytic reaction (Yu et al., 2019, Alpdagtas et al., 2022). Metal-independent FDHs are found in some bacteria and archaea, and are involved in the catabolism of various compounds, including formate, formaldehyde, and methanol. Metal-containing FDHs enzymes require metal cofactors for their activity and can be further divided into several subtypes based on the specific metal involved. The most common metal cofactors in FDHs are molybdenum (Mo), tungsten (W), and iron (Fe). Molybdenum-containing FDHs utilize a molybdopterin cofactor to transfer electrons during the catalytic reaction. The molybdenum cofactor consists of a molybdenum ion coordinated with a pterin molecule and is involved in the oxidation or reduction of various substrates. Molybdenum-containing FDHs are found in bacteria, archaea, and some eukaryotes. They are involved in the catabolism of various compounds, including formate, formaldehyde, and methanol (Calzadiaz-Ramirez and Meyer 2022). Tungsten-containing FDHs utilize a tungsten cofactor to transfer electrons during the catalytic reaction. The tungsten cofactor consists of a tungsten ion coordinated with a dithiolene ligand and is involved in the oxidation or reduction of various substrates. Tungsten-containing FDHs are found in certain bacteria and archaea (Yang et al., 2022). They are involved in the catabolism of formate and other compounds and can also catalyze the reduction of CO_2 to formate (Yan et al., 2023). Both molybdenum and tungsten are transition metals with similar chemical properties, and they can substitute for each other in certain enzymes. However, molybdenum is more commonly found in nature and is more extensively studied than tungsten. Researchers continue to investigate the roles and mechanisms of molybdenum- and tungsten-containing FDHs in various biological processes and their potential applications in biotechnology (Schoepp-Cothenet et al., 2012).

1.4. Biological pathway of FDH in microbes

FDH, or formate dehydrogenase, is an enzyme that plays an essential role in the metabolism of microbes. It is involved in the oxidation of formate to carbon dioxide, which is an important step in various biological pathways such as carbon fixation, energy production, and anaerobic respiration (Appel et al., 2013). The biological pathway of FDH in microbes involves several steps. (i) Formate uptake: Microbes can take up formate from the environment through specific transporters. (ii) Formate oxidation: Once inside the cell, formate is oxidized by FDH, catalyses formate conversion to carbon dioxide and electrons. The electrons produced in this reaction are transferred to the electron transport chain, where they are used to generate ATP. (iii) Electron transport: The electrons produced by FDH are transferred to various electron carriers, such as NAD^+ or FAD. These electron carriers then donate their electrons to the electron transport chain, which generates a proton gradient across the cell membrane. This gradient is used to drive ATP synthesis. (iv) Carbon fixation: In some microbes, the carbon dioxide produced by FDH is used in the carbon fixation process, where it is converted into organic compounds such as sugars or amino acids. (v) Anaerobic respiration: In anaerobic conditions, some microbes can use FDH to generate energy by using alternative electron acceptors such as nitrate or sulfate (Parkin et al., 2007).

1.5. Proteins involved in FDH pathway

Formate utilization begins with oxidation to carbon dioxide and then enters the CO2 reduction pathway, which is catalysed by formate dehydrogenase. Molybdenum as a molybdoprotein cofactor, flavin adenine dinucleotide (FAD), zinc, iron, inorganic sulphur, and two different subunits in a configuration may be present (Burgdorf et al., 2001). Anaerobic bacteria can metabolize C1 carbon molecules. As intermediates in this metabolism, formaldehyde, formyltetrahydrofolate, formate, and a methyl corrinoid are assumed. Four moles of formate results in three moles of carbon dioxide and one mole of methane when used as a substrate (Yang et al., 2022). For energy, anaerobic bacteria like *Clostridium thermoaceticum* and others that feed on carbohydrates or purines use carbon dioxide (CO_2) as an electron acceptor and produce acetate. Formyltetrahydrofolate is synthesized from CO_2 by formate dehydrogenase, with formyl tetrahydrofolate synthetase serving as an intermediary (Berrios-Rivera et al., 2002). Enterobacteriaceae break down carbohydrates anaerobically to pyruvate, which is further broken down to acetyl-CoA or acetyl phosphate and formate. Pyruvate is broken down into formate by the enzyme pyruvate formate lyase. Primarily, formate is a precursor for the 2- and 8-carbon positions of purines, the S-methyl group of methionine, and the methyl group of thymidine. Small amounts of formate are generated during the production of D-*erythro*-dihydroneopterin triphosphate from GTP (Haussmann et al., 1998).

1.6. Function of formate dehydrogenase

The enzyme formate dehydrogenase (FDH) converts formate to carbon dioxide while reducing a cofactor like nicotinamide adenine dinucleotide phosphate ($NADP^+$) or nicotinamide adenine dinucleotide (NAD^+). FDH's main job in living things is to produce energy. In bacteria, for example, FDH is involved in the anaerobic metabolism of formate as an energy source (Sanchez et al., 2005). In this process, formate is oxidized to carbon dioxide, releasing electrons that are used to produce ATP through the electron transport chain. FDH also plays a role in carbon dioxide fixation in certain organisms, such as methanogens, which use formate as a precursor for methane biosynthesis (Niu et al., 2023). In these organisms, FDH is involved in the reduction of carbon dioxide to formate, which is then used as a substrate for methanogenesis. Additionally, FDH has been found to play a role in the detoxification of formate in certain organisms, such as mammals. In humans, for example, FDH is involved in the metabolism of formate, which is a toxic byproduct of methanol metabolism (Steiniger et al., 2022). In this process, formate is oxidized to carbon dioxide and water, which the body can safely excrete. Formate dehydrogenases, a broad family of enzymes in both prokaryotes and eukaryotes, catalyse formate oxidation to carbon dioxide. Formate may be used efficiently by many hydrogenotrophic methanogens in place of H2, while the latter cannot. Formate dehydrogenases are enzymes that catalyze the reaction in methanogens that convert formate to reduced coenzymes during oxidation (Kurt and Ordu 2021).

1.7. Structure of FDH

Formate dehydrogenase (FDH) is a large enzyme typically consisting of several subunits. The exact structure of FDH varies among different organisms, but generally, it consists of a catalytic subunit, a cofactor-binding subunit, and often a membrane-spanning subunit. The catalytic subunit contains the active site where formate oxidation takes place, and it typically has a molybdenum cofactor (Moco) or tungsten cofactor (Wco) bound to it. The cofactor-binding subunit binds the electron-transfer cofactor (e.g., NAD^+ or $NADP^+$) and transfers the electrons to the catalytic subunit (Sosa Torres and Kroneck 2020). The membrane-spanning subunit anchors the enzyme to the cell membrane, as FDH is often located on the cytoplasmic membrane. Overall, the structure of FDH is highly complex and can vary greatly depending on the organism in which it is found. The enzyme may exist in different conformations depending on whether it is in an active or inactive state, and it may undergo conformational changes during the catalytic cycle (Jormakka et al., 2008). FDH is used to regenerate NADH in enzymatic syntheses of optically active compounds. This enzyme belongs to the D-specific 2-hydroxy acid dehydrogenase superfamily. The catalytic mechanism of the dehydrogenase enzyme is defined by the direct transfer of a hydride ion from the substrate to the C-4 atom of the nicotinamide moiety of NAD^+ (Schirwitz et al., 2007). Numerous studies have demonstrated the importance of FDH in enzymatic processes, particularly those involving the replenishment and decrease of cofactors. The amino acid residues responsible for catalysis in the active site of each of these enzymes are extremely well conserved. Alcohol dehydrogenase (ADH), lactate dehydrogenase (LDH), malate dehydrogenase (MDH), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) are the most used enzymes in mechanistic investigations, despite NAD^+ dependent dehydrogenase being one of the most researched proteins (Xie et al., 2020). The catalytic domain is the region of a protein that performs the actual catalytic reaction. The subunit interface is a coenzyme-binding region that is centrally placed along the polypeptide chain. The dimer's two catalytic domain pieces are spatially separated and do not interact with one another. The two domains are linked by two long α-helices, αA and α8. In the secondary structure of NAD^+-dependent FDH, each domain has the same type of structural organization, showing a left-handed twisted parallel β-sheet surrounded by α-helices. The coenzyme binding domain consists of seven standard β-sheets and the catalytic domain consists of five standard β-sheets with two short antiparallel strands (Lim et al., 2022). Formate is oxidized to carbon dioxide (CO_2) by molybdenum-containing NAD^+-dependent formate dehydrogenases found in bacteria like *Ralstonia eutropha*, which also reduce NAD^+ to NADH and other members of the NADH dehydrogenase superfamily of enzymes. Its spatial arrangement of many redox-active centers and structural similarity to a comparable subunit of NADH dehydrogenase's matrix- or cytosol-exposed region are striking (Niks et al., 2016).

1.8. Role of metal ions in FDH

FDH is an enzyme that catalyses the conversion of formate to carbon dioxide, coupled with the reduction of an electron acceptor such as NAD^+ or a quinone. Metal ions play a crucial role in the catalytic activity of FDH by assisting in the transfer of electrons and in stabilizing the enzyme structure. One important metal ion in FDH is molybdenum, which is a part of the enzyme's active site (Alekseeva et al., 2011). Molybdenum interacts with the formate substrate, assisting in its deprotonation and subsequent oxidation to CO_2. Molybdenum also plays a role in the transfer of electrons from formate to the electron acceptor. Another metal ion that can be involved in FDH is iron-sulfur clusters. These clusters help to transfer electrons during the catalytic reaction and can also contribute to stabilizing the enzyme structure (Bulut et al., 2020). Other metal ions that have been shown to play a role in FDH activity include calcium, magnesium, and zinc. Calcium and magnesium are involved in stabilizing the enzyme structure, while zinc can transfer electrons. In FDH, metal ions play important roles in the catalytic activity and stability of FDH (Talekar et al., 2022). Molybdenum is an essential metal ion in the enzyme's active site, while iron-sulfur clusters, calcium, magnesium, and zinc can also contribute to the enzyme's function. Formate dehydrogenases (FDHs)

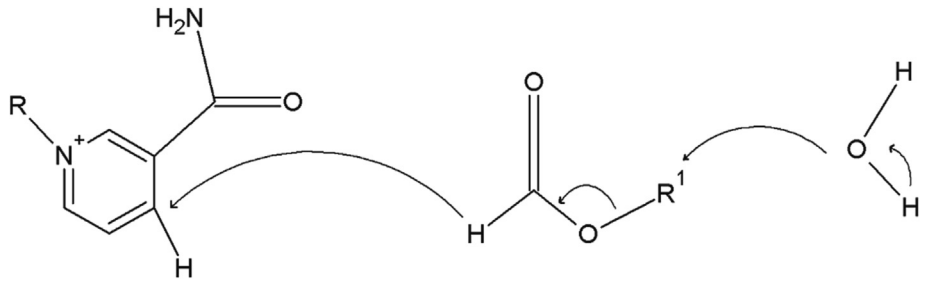

Fig. 1. Explicitly demonstrates the putative catalytic mechanism for NAD^+-mediated hydride transfer from formic acid and formic acid esters.

in prokaryotes are metalloproteins that catalyze the oxidation of formate anion to carbon dioxide via a redox mechanism involving the transfer of two electrons from the substrate to the active site. Four sulfur atoms from two pyranoprotein molecules, one selenium atom from selenocysteine (SeCys), and one inorganic sulfur atom form a deformed trigonal prismatic geometry around a hexacoordinated molybdenum or tungsten ion in the active site of this metal-dependent dehydrogenase. Many bacteria that thrive in sulfide-rich environments have been found to have molybdenum FDHS as well as tungsten FDHS, albeit the molybdenum level is likely to be lower than that of tungsten due to the very poor solubility of molybdenum sulphides (Dong and Ryde 2018). Thermophilic bacteria and hyperthermophilic archaebacteria both have enzymes containing tungsten. Tungsten enzymes, like molybdenum enzymes, fall into one of three families; each of these families contains two pterin cofactor molecules for every molybdenum atom. They share similarities with the molybdenum enzyme family that reduces DMSO. The first two classes catalyze different types of redox reactions. The redox processes are catalyzed by the first two members of this family. Before transferring reducing equivalents to a [4Fe-4S] center, the aldehyde oxidoreductase family catalyzes the oxidation of aldehydes to carboxylic acid (Kisker et al., 1997).

1.9. Catalytic mechanism of formate dehydrogenase

The catalytic mechanism of formate dehydrogenase (FDH) involves the transfer of electrons from formate to an electron acceptor, such as NAD^+ or a quinone, with the concomitant conversion of formate to carbon dioxide. The active site of FDH contains a molybdenum cofactor, which is essential for catalytic activity. The molybdenum ion can exist in several oxidation states, but during the catalytic cycle of FDH, it is in the Mo(VI) state (Tishkov and Popov 2004). The catalytic mechanism of FDH can be divided into several steps: (i) Binding of formate: The formate substrate binds to the molybdenum cofactor in the active site of FDH, forming a complex that is stabilized by hydrogen bonding and electrostatic interactions. (ii) Deprotonation of formate: The formate substrate is deprotonated by a basic residue in the active site, forming a negatively charged intermediate. (iii) Transfer of electrons: The negatively charged intermediate is then oxidized by the molybdenum cofactor, which accepts two electrons and two protons from the formate substrate. The oxidation of formate to carbon dioxide is coupled with the reduction of the molybdenum cofactor from the Mo(VI) state to the Mo(IV) state. (iv) Transfer of electrons to the electron acceptor: The reduced molybdenum cofactor then transfers the two electrons to the electron acceptor, which is reduced in the process. (v) Release of products: The products of the reaction, carbon dioxide and the reduced electron acceptor, are released from the active site, and the enzyme is ready to catalyze another reaction (Li et al., 2021, Popinako capital A et al., 2022, Meneghello et al., 2023). Frohlich et al. proposed the working hypothesis of hydrogen transfer catalysis based on undissociated formic acid. Concurrent nucleophilic attack of water on the acid proton facilitates the hydride transfer to NAD^+ (Frohlich et al., 2011). Cleavage of formic acid esters is a straightforward example of this hypothesis in action; in this case, the water molecule attacks the C1 atom of the alkyl or aryl residues in the substrate, resulting in the production of $NADH^+$, CO_2, and the corresponding alcohol (Fig. 1). Formate dehydrogenase is a crucial cofactor regenerator among the several NAD (P)H-dependent oxidoreductases utilized in biocatalysts and biotransformation. However, the main issue is that most naturally occurring FDHs have poor catalytic activity and operational stability. A selenocysteine residue at the molybdenum core is essential to its catalytic activity, which is why it does not catalyze oxygen atom transfer events but successfully breaks a C—H bond (Schmidt et al., 2010, Srikanth et al., 2017). As efficient and reversible electrocatalysts for CO_2 reduction, metal-dependent formate dehydrogenase enzymes have recently come to the fore. Enzymes with Mo atoms have been discovered in almost every known living organism. However, their atomic and ionic radii and coordination chemistry are very similar (Karaguler et al., 2007, Alissandratos et al., 2013).

1.10. Amino acid and its role in the catalytic site of FDH

FDH's catalytic region is rich in amino acids that contribute to the enzyme's activity. A thiolate-imidazolium ion pair is formed between a histidine residue and cysteine in the catalytic region of FDH, making cysteine an essential amino acid (Yang et al., 2020). This pair stabilize the formate intermediate generated during the reaction. Tryptophan is also significant since it is a proton acceptor in the process (Zhang et al., 2018). Tryptophan accepts the proton that is produced during the oxidation of formate to carbon dioxide and water. FDH's catalytic region also contains the amino acids serine, aspartate, and lysine, which all play important roles in substrate binding and electron transfer. The catalytic domains of FDH (residues 400–902) were analysed from a gene related to aldehyde dehydrogenase and are in charge of the oxidation of short-chain aldehydes to their corresponding acids. An intermediate linker connects two catalytic domains (residues 311–399). In the FDH mechanism, this intermediate linker domain shuttles a formyl from the N-terminal domain to the C-terminal domain, where it is covalently linked to the sulfhydryl group of the phosphor pantetheine arm. A number of different investigations has established FDH's catalytic domain (Karaguler et al., 2007).

1.11. Role of selenium-Cys in the catalytic site

In three different classes of bacterial enzymes-glycine reductase in a few clostridia, formate dehydrogenases in *Escherichia coli, salmonella Clostridia*, and a *Methanococcus*, and hydrogenases in *Methanococcus* and a few other anaerobic bacteria—selenocysteine is found in a very unique position (Eswayah et al., 2016). Nearly half of all proteins in nature are metalloproteases, and many of these proteins, including zinc finger proteins, blue copper proteins,

azurine iron-sufur proteins, and others, utilise cysteine thiolates as ligands for their metal cofactors (Jiang and Lewis 2023). Several metalloenzymes, such as formate dehydrogenase and nitrate hydrogenase, use selenocysteine to coordinate metal ions. The C-se bond in selenocysteine is weak and can be quickly weakened under mild conditions, making it a useful precursor to other amino acids (Kumar et al., 2023). The catalytic activity of *E. coli* formate dehydrogenase H relies on a selenocysteine residue (SeCys-140 in the polypeptide chain), in addition to molybdenum, two molybdopterin guanine dinucleotide cofactors, and selenocysteine (Boyington et al., 1997, Khangulov et al., 1998). The crystal structure indicates that it consists of three subunits such as α, β, and γ. The catalytic subunit is made up of 982 amino acids, one of which is an inherent selenium cysteine (SeCys) residue found in their active sites (Maia et al., 2015). Changing the TGA codon to TGC results in a mutant variant of the enzyme [S] FDHH that contains Cys rather than SeCys. The enzyme's catalytic activity was drastically reduced due to the substitution of sulfur for serine (Ser) since the mutant version of the enzyme containing SeCys was catalytically inactive. The formate-hydrogen lyase complex selenoenzyme of *Escherichia coli* oxidizes formate to CO_2 and decreases equivalents that are passed to a hydrogenase. A free selenolate anion is formed when formate binds to molybdenum, which then displaces selenocysteine, releasing CO_2 and transferring two electrons to the molybdenum center (Hartmann et al., 2015, Fogeron et al., 2022).

1.12. Reaction mechanism of FDH

The anaerobic molybdoenzyme formate dehydrogenase oxidizes formate to carbon dioxide. At the density functional level in both vacuum and protein settings, two primary mechanisms have been examined to elucidate the process of catalysis in molybdoenzyme; these mechanisms differ in whether a SeCys residue directly coordinates to the molybdenum metal during catalysis (Leopoldini et al., 2008). The oxidation of formate is a major electron source for many pathways in anaerobic prokaryotes that use molecules other than dioxygen as final electron acceptors. The oxidation reaction releases two protons from small, neutral compounds like formic acid that have diffused across the cytoplasmic membrane into the periplasmic region. Kinetic and spectroscopic studies of *E. coli* FDH-H demonstrate that the oxidation of formate requires the breaking of the C—H bond to yield a CO_2 molecule, and that the proton of the substrate is transferred to an acceptor group near the molybdenum ion (Hartmann et al., 2016). The SeCys residue serves as the proton acceptor group in both suggestions, but the molybdenum formate interaction is accomplished quite differently in the two models. Raaijmakers proposed that the formate active site interaction takes place along the catalytic cycle after the Se═Mo link is broken with the Si ligand bound to molybdenum. Methane, methanol, and formate all support yeast and aerobic growth (Jormakka et al., 2003). Methanol, formaldehyde, formylglutathione, and formate are intermediates in the energy metabolism of these organisms, which ultimately results in carbon dioxide. Three moles of carbon dioxide and one mole of methane are produced from four formate moles when serving as the formate act substrate. After being oxidized to CO_2, the formate is converted to methane. Most likely, CO_2 is converted to formate as the first step. Then, the free formate could play a role in the production of methane (Friedebold and Bowien 1993).

1.13. Electron transfer reaction

Formate and hydrogen play pivotal roles in interspecies electron transfer in methanogenic environments. Hydrogen molecules are crucial in microbial metabolism because their midpoint redox potentials are similar to those of the redox couples $H2/H^+$ and formate/CO_2, despite the fact that hydrogen and formate have different chemical and physical properties. When methane formation in syntrophic butyrate-degrading cultures from a reactor treatment could not be accounted for by interspecies hydrogen transfer alone, experiments showed that formate might be involved for electron transfer (Schuchmann et al., 2018). The most common C-type cytochrome C3 accepts electrons from periplasmic formate dehydrogenases to complete the reduction of quinine and is a physiological partner of periplasmic hydrogenases. Sulfate reduction in the cytoplasm requires electron transfer from the periplasmic dehydrogenases to membrane-bound complexes containing cytochrome C. When fumarate is added, menaquinone in the membrane of *W. Succinogenase* is reoxidized. Menaquinone's redox state is determined by formate dehydrogenase activities in the steady-state of electron transfer. Subunit and prosthetic group compositions are identical in the crystal structure of formate dehydrogenase-N from Escherichia coli (Heidelberg et al., 2004). The catalytic subunit carries four tetranuclear iron-sulfur clusters localized at an appropriate distance for rapid electron transfer from the molybdenum site to yield two electrons, CO_2 and a proton. While the electron transfer to the ion cluster, CO_2 and protons leaves the catalytic site via substrate crevice and also the *E. coli* encodes the another structurally related formate dehydrogenase isoenzymes such as formate dehydrogenase-O (FdhO/FdoGHI) that are known to acts as electron transfer sinks which required for oxidation of formate to CO_2 and H^+ and plays a role in the electron transfer to nitrate reductase (Holm and Lo 2016, Kim et al., 2016).

1.14. The sulfur shift: An activation mechanism for formate dehydrogenase

The sulfur shift is an activation mechanism for formate dehydrogenase (FDH) that involves a unique conformational change in the enzyme's active site. This mechanism is used by certain variants of FDH, such as the molybdopterin-containing FDH from the bacterium *Rhodobacter capsulatus*. In the sulfur shift mechanism, a conserved cysteine residue in the enzyme's active site undergoes a reversible oxidation to a persulfide (R-S-S-H) state (Mardina et al., 2016, Dong and Ryde 2018). This persulfide intermediate then reacts with the formate substrate, forming a covalent thioformate intermediate (R-S-CO_2). The covalent thioformate intermediate is then rearranged in a process known as the sulfur shift, which involves the transfer of the thioformate group to a neighboring sulfur atom in a molybdopterin cofactor. This results in forming a new molybdopterin-sulfur linkage and releasing carbon dioxide and a thiol. The sulfur shift mechanism has been proposed to increase the rate of formate oxidation by facilitating the transfer of the formate group to the molybdopterin cofactor. This mechanism is thought to be particularly effective in FDH variants that lack a conserved arginine residue in the active site, which is thought to play a similar role in other FDH variants. The density functional theory calculation revealed that mainly three combinations of three simulations primitive charge are involved in sulfur shift mechanism; 1) the unbinding of Cys140 in Nap and SeCys140 in FDH from the shell to the second shell of the molybdenum ion and interact very closely with each other forming a quasi-covalent bond, 2) charge of the coordination position of the sulfide to the place previously occupied by the residue and the coordination of the substrates to the MO ion, 3) this process opens free coordination position at the metal site that is promptly occupied by the substrate that is, nitrate in Nap and formate in FDH (Fig. 2). The sulfur shift mechanism also found in other mechanistic proposals; Hofmann showed that nitrate reaction with a persulfate molybdenum complex fragment is favored over the oxidation of molybdenum bound sulfur atom (Cerqueira et al., 2013).

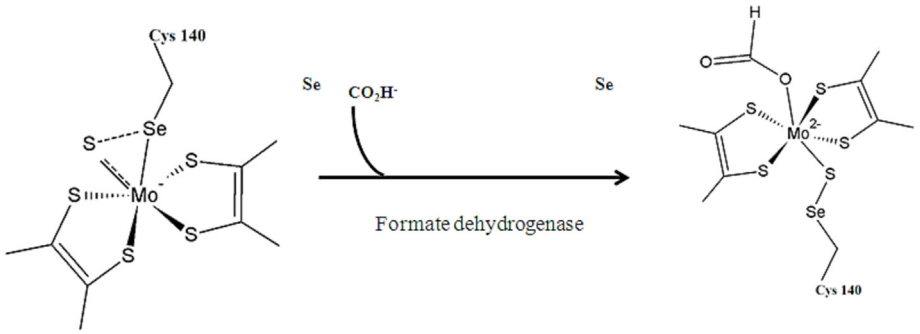

Fig. 2. Represent the Sulfur shift mechanism of formate dehydrogenase.

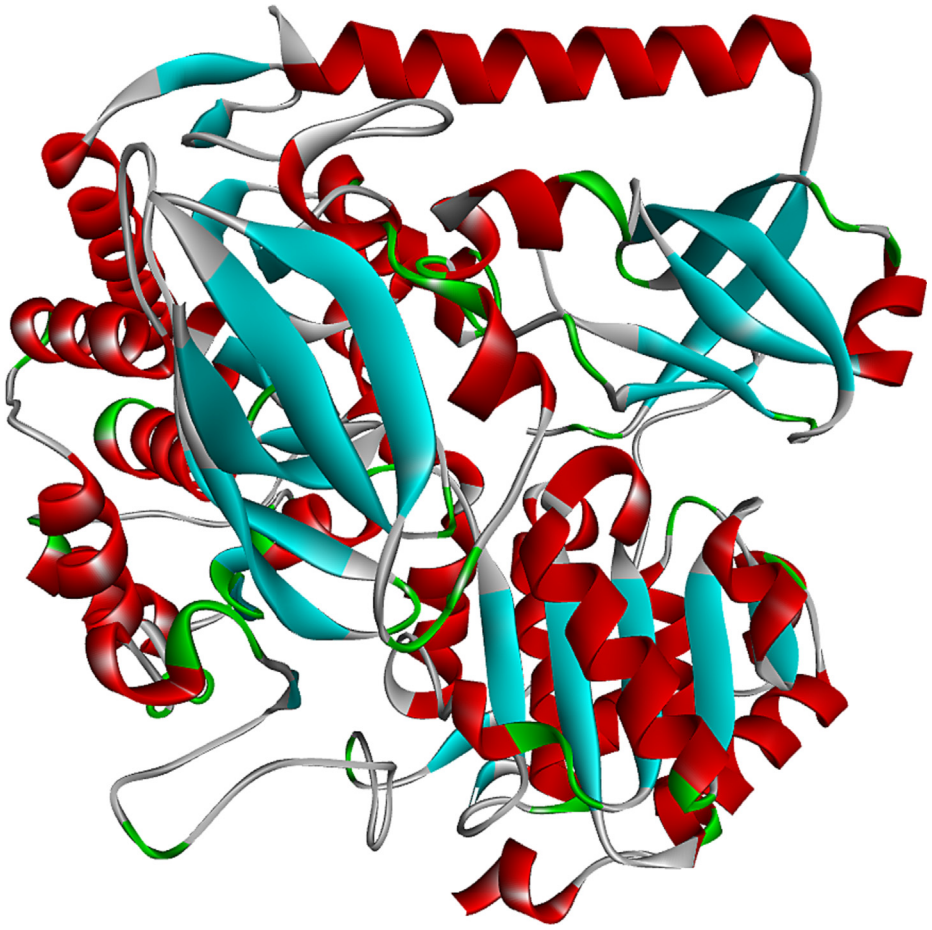

Fig. 3. Shows the structural representation of FDHH of *E. coli*.

1.15. Comparative analysis of structure of FDH

The first and native structure NADP –dependent FDH identified in proteobacterium *Burkholderia stabilis*. It shows lower affinity and accepts both phosphorylated cofactor and NAD^+. Recently Fogal et al. characterized new structural information on FDH from *Granulicella mallensis* (GraFDH). It contains the common feature of bacterial formate dehydrogenase with two monomers, each having a cofactor binding or catalytic domain. In addition, feature of secondary structure and tertiary structure analysis revealed that the GraFDH is the closest homolog of *Pseudomonas sp*. 101 (Singh et al., 2018). It shares several enzymatic features including contact area due to long loop protruding from each 1L and 4L hydrogen bond. Similar to *Pseudomonas sp*.101 GraFDH also shows the complex with $NADP^+$ and NaN3, however the sequence of GraFDH is shorter than *Pseudomonas* and *Moraxella* enzyme those have 10 to 11 amino acids longer (Fogal et al., 2015). The crystal structure of *Candida boidinii* FDH (CbFDH) composed of two domains named as NAD binding or catalytic domain consist of 15 α-helices and 13 β-strands like all the member of dehydrogenase family. The catalytic domain of the CbFDH shows the Rossmann fold structure with three layer of polypeptide chain. Both the domains are connected by two long helices (H6 and H15) where the active site residues are located (Tishkov and Popov 2004).

In case of the structure of formate dehydrogenase H of E coli contains more than two cofactors such as selenocysteine, molybdenum and two molybdopterin dinucleotide (MGD) cofactors. In addition, Fe4S4 cluster is present in the active site responsible

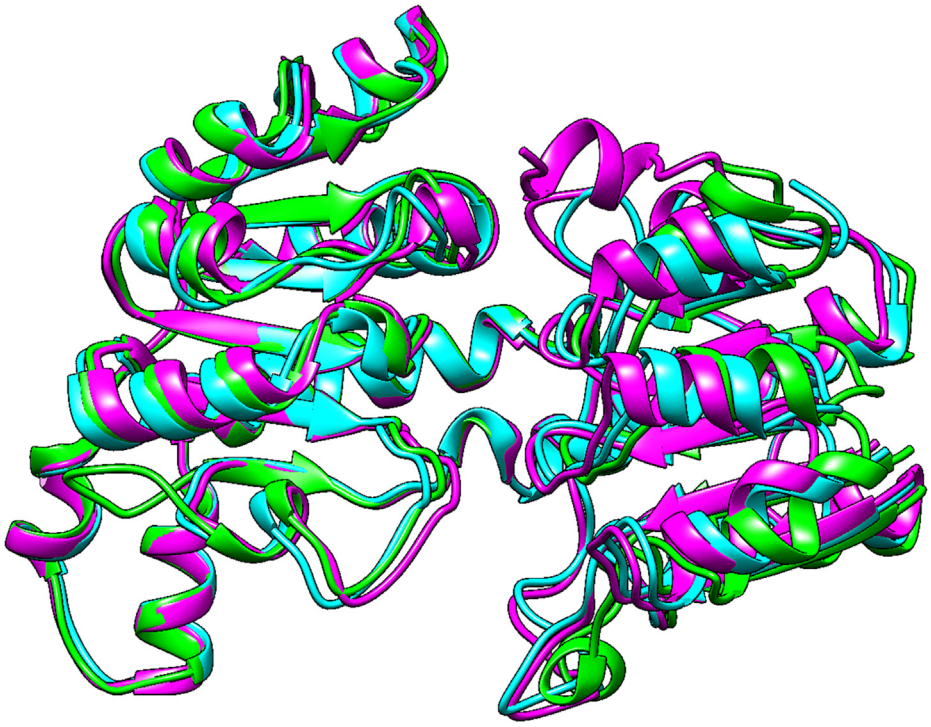

Fig. 4. Structural comparison of structure of CbFDH (green; PDBID: 2FSS), PseFDH (Cyan; PDB ID: 2GO1) and GraFDH (Megenta; PDB ID: 4XYB).

for catalyzing the oxidation of formate to carbon dioxide. The crystal structure of FDHH from *E. coli* shows four αβ domains (Fig. 3) with small antiparallel β-sheets. The MGD domain II and III closely resemble the classical dinucleotide binding fold. Recently new interpretation of the FDHH of *E. coli* was evaluated with new reaction mechanism. The FDH of methyltrophic bacteria Pseudomonas sp. has two globular domains (domain I and II). The first domain is formed by the residues 147–333 responsible for the NAD^+ binding, and the second domain acts as catalytic domain formed by the residues 1–147 and 333–347. The FDH structure of Desulfovibrio gigas is the first reported tungsten containing enzyme. It consists of three subunits (α, β and γ), the larger subunit is similar to the FDH of the *E. coli* and have the essential conserved residues such as SeCys158, His159 and Arg407 at the active site (Selvaraj et al., 2014). The α and β subunits is similar to FDH of Desulfovibrio vulgaris Hildenborough, however instead of tungsten those have molybdenum with MGD, SeCys cofactors and 4Fe-4S cluster. Molybdenum containing FDH plays a key role in different metabolic pathways and electron transfer due to the presence of FeS cluster. The sequence similarity of the above-mentioned structure shows in Fig. 4 and the structural comparison represented in Fig. 5.

2. Concluding remarks and future prospective

A key enzyme in the process of CO_2 reduction by microorganisms is formate dehydrogenase (FDH). The potential of microbial FDHs in the creation of CO_2 reduction technologies has been investigated in recent years. Combining electrochemical systems with FDHs is one strategy for producing sustainable fuels and chemicals. Immobilized FDHs on electrodes catalyze the conversion of carbon dioxide to formate or other organic compounds in this method. Microbial FDHs have been investigated for the synthesis of formate as a chemical feedstock in addition to their application in electrochemical systems. In order to manufacture huge amounts of formate, scientists have engineered E. coli strains by overexpressing FDH and other enzymes involved in formate metabolism. More than 80% of formate dehydrogenase sequences are identical in closely related bacterial species. The use of formate as an intermediate and one of the most promising agents for CO_2 reduction has garnered more attention in recent years. Since then, various types of efficient catalysts have allowed for the development of technology for both the reduction of CO_2 and its usage. The reduction of formic acid and carbon dioxide is catalyzed in part by the biocatalyst formate dehydrogenase. One prospective method of producing formate in the future is by the use of bacterial FDH; in general, the non-enzymatic electrochemical reduction of CO_2 necessitates the high electrode potential. Therefore, effective biocatalysts FDH from various microorganisms have been utilized recently to address these issues. Oxygen sensitivity necessitates the employment of other Mo-containing FDHs, many of which are very resistant to oxygen and make it simple to manufacture the stable form of formate in large quantities. The hydrogenation of CO_2 and the formation of formate were catalyzed by another complex enzyme from Acetobacterium woodii, which was 1500 times more potent than a chemical catalyst. The essential involvement of specific amino acid residues in the catalytic mechanism of FDH will be investigated by a number of protein engineering and mutational experiments. This means that FDH could serve as a model enzyme for research into future applications of whole-cell catalysis for efficient CO_2 hydrogenation. Overall, this review narrates the detail elucidation of molecular level information of Formate Dehydrogenase, and this information's will be huge impact in understanding the FDH in the event of CO_2 reduction mechanism.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

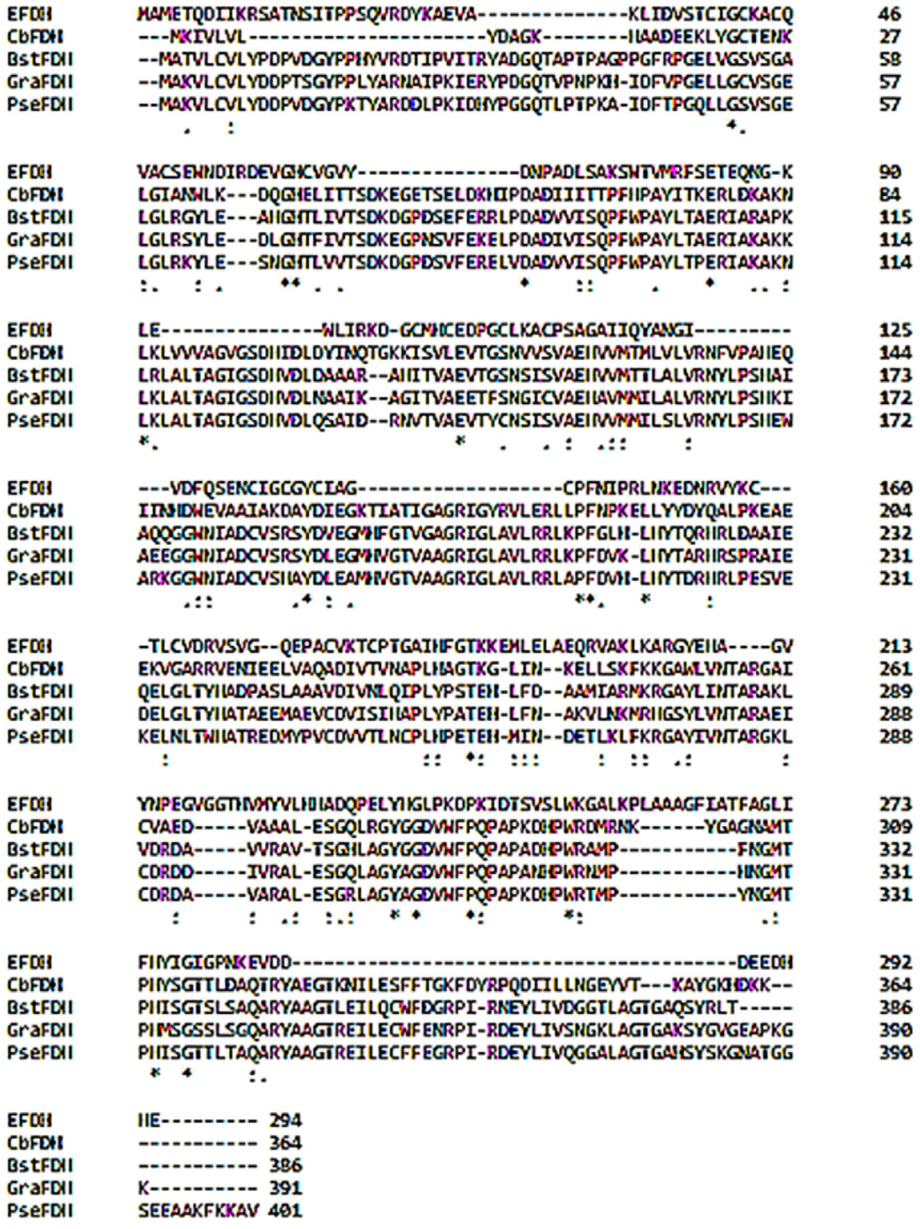

Fig. 5. Sequence alignment of formate dehydrogenase enzymes of from bacteria CbFDH, GraFDH, PseFDH, FDH of *E. coli*, BstFDH. (*) symbol denoted the conserved amino acids and (:) symbol denotes the semi-conservative substation.

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