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Review Article

STUDY ON INCREASING SOLUBILITY OF ISOLATES: METHODS AND ENHANCEMENT POLYMERS

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ABSTRACT

Natural ingredients have been a source of medicine since ancient times. Research on the development of natural ingredients as medicinal ingredients has increased. One of these is isolating active substances from herbs in a pure state (isolate). However, some problems hinder the use of isolates as the primary treatment option, one of which is solubility. Most isolates had poor solubility, inhibiting the body's absorption process. This review investigates the method and polymer to increase the solubility of isolates and summarizes the development of drugs from isolates. This review also explains how effectively the method and polymer improve the solubility or dissolution of the isolate. We expect the results to be a reference for research on isolates with poor solubility.

Keywords: Solubility, Isolate, Solubility enhancement method, Polymer

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INTRODUCTION

Natural ingredients have been used as a source of medicine since ancient times. They were using natural materials that coincided with the beginning of human life on earth. Humans needed natural materials as staple food and as medicine. Using drugs from natural ingredients based on empirical results is carried out from generation to generation. It is recorded as far back as 5000 BC in Sumerian, Egyptian, Greek, and Roman cultures [1]. Drugs from natural ingredients are usually still in an impure form containing several constituents believed to have a synergistic effect on producing the desired therapy [2]. Currently, medicinal preparations from natural ingredients continue to be developed and researched to overcome various diseases. However, there are problems with the use of natural materials. One is poor solubility, especially in water, due to using nonpolar or semi-polar solvents during the extraction process to isolation [3].

Table 1: Solubility classification based on farmakope Indonesia VI [4]

Solubility definition	Part of solvent required for one part of solute (g/ml)
Very soluble	<1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10.000
Practically insoluble	>10.000

Solubility is the maximum amount of a substance that can be dissolved in a certain amount of solvent at a given temperature [5]. Quantitatively defined as a solute concentration in a saturated solution at a specific temperature [6]. Solubility depends on the characteristics of the solvent, temperature, and pressure. The solvent can be a single liquid or a combination of liquids, where the characteristics of the solvent will affect the solute, polar solvents will dissolve polar substances, and nonpolar solvents will dissolve nonpolar substances [5]. Polar substances easily dissolve in water but have poor membrane permeability [7]. The pH level of the solvent affects the solubility of substances, acidic substances will be more soluble in alkaline solvents, and alkaline substances will more easily dissolve in acidic solvents; the ionization process influences this. Particle size affects the solubility of a substance; the smaller the particle size, the easier the substance is dissolved in the solvent because of the more significant the surface area of the substance. The form of a substance also affects solubility; crystalline forms will be more difficult to dissolve than amorphous ones [5].

Solubility is one of the main parameters in the rate of absorption, dissolution, and bioavailability. Drug absorption through the oral and parenteral routes will be affected by its solubility in water [8]. Dissolution is an *in vitro* drug release test required to simulate the release rate of solid or semisolid drugs into a liquid solvent under standardized temperature, stirring, velocity, volume, and media composition [9]. Meanwhile, bioavailability is the rate and amount of the active drug substance absorbed and available at the drug's site of action. The drug absorbed rate and the amount is usually measured by AUC and Cmax (maximum concentration) [10]. The results of *in vivo* bioavailability testing will be influenced by the solubility of the drug in water [8].

Table 2: Isolate solubility data

Isolate	Solubility in water	Solubility class	Reference
Curcumin	1.34±0.02 mg/l	Practically insoluble	[11]
Piperine	2.93 µg/ml	Practically insoluble	[12]
Quercetin	0.21±0.14 µg/ml	Practically insoluble	[13]
Andrographolide	0.10 mg/ml	Very slightly soluble	[14]
Rutin	0.045±0.002 mg/ml	Practically insoluble	[15]
Myricetin	16.60±0.92 µg/ml	Practically insoluble	[16]
Daidzein	3.84±0.13 µg/ml	Practically insoluble	[17]
Naringenin	43.83±0.039 µg/ml	Practically insoluble	[18]
Luteolin	2.5 µg/ml	Practically insoluble	[19]

Table 3: Isolate dissolution data

Isolate	Dissolution	Reference
Curcumin	Intrinsic: 7.96 x 10^{-3} mg/cm^2. minute in 40% Ethanol	[20]
Piperine	45.30% at minute 60 in water	[12]
Quercetin	1.1% at minute 60 in phosphate buffer	[21]
Andrographolide	20% at minute 60 in water	[22]
Rutin	22% at minute 120 in SLS 0.1% pH 1.2	[15]
Myricetin	Intrinsic: 9.89 µg/cm^2. minute in water	[23]
Daidzein	5.30% at minute 45 in water	[24]
Naringenin	22% at minute 120 in water	[25]
Luteolin	13.11% at minute 90 in 0.1 N HCl	[26]

Different processes or modifications of the isolate were carried out to increase the solubility. Solid dispersion, inclusion complex, micelles, cocrystals, and nanosuspensions are various methods to increase solubility. This review will describe the methods that can increase the solubility of isolates. The increase in solubility can be assessed from the isolate's solubility, dissolution, and bioavailability tests.

MATERIALS AND METHODS

The writing of this article began in February 2021 through journal searches on Google Scholar and Pubmed using the keywords "Improvement of isolate solubility" or "Solubility Enhancement of Isolate." The inclusion criteria of this journal are the results of research that developed a method of increasing the solubility of isolates with solubility or dissolution testing published in 2013-2022. Exclusion criteria are journals that are the result of a review with a related theme and which cannot be accessed entirely.

RESULTS

Solubility enhancement method

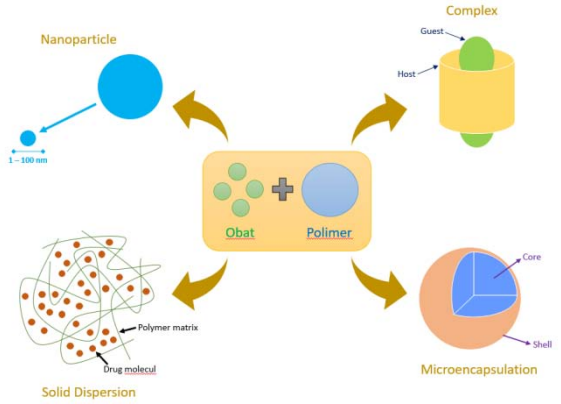

Fig. 1: Solubility enhancement method in isolate (designed by authors)

Nanoparticle

In recent years, nanoparticles have been widely used in pharmaceuticals, significantly increasing drug solubility [27]. Nanoparticles are defined as particles having a size of 1-100 nm, of which 50% of the particle distribution should be in this range [28]. Nanoparticles can be a solution to overcoming problems in drugs derived from herbal plants [29]. Reducing the particle size will increase the solubility of the particles because it increases the surface area and reduces the thickness of the protective layer of the particles [30]. It is proven by testing the dissolution of drugs belonging to the BCS class II class, namely hydrochlorothiazide, aceclofenac, and ibuprofen, with a size of<150 nm, with more drugs dissolved in the dissolution medium than the larger size [31].

Nanoparticles consist of several types distinguished from the material of manufacture and the system. Liposomes are the first generation of nanosized drug delivery systems [32]. Liposomes are nanosystems formed from a hydrophilic core surrounded by one or more phospholipid bilayers [33]. This phospholipid bilayer is usually biodegradable and biocompatible lipids, such as glycerophospholipids and phosphatidylcholine. Liposomes have become valuable medication delivery devices because they can encapsulate hydrophilic or lipophilic active compounds [34]. An example of the use of liposomes in isolates is curcumin, where curcumin is insoluble in water [35]. Curcumin is the main constituent of the Curcuma longa plant, commonly called turmeric [36]. Liposomes of curcumin were prepared using the thin film hydration method, in which curcumin (200 mg), cholesterol (500 mg), and soybean lecithin (500 mg) were dissolved in a mixed solvent of methanol: chloroform (1:9) which was shaken to form a thin layer of oil. The results of the curcumin liposome test showed that the drug release in phosphate buffer pH 7.4 (with dialysis membrane) reached 70.96% [37].

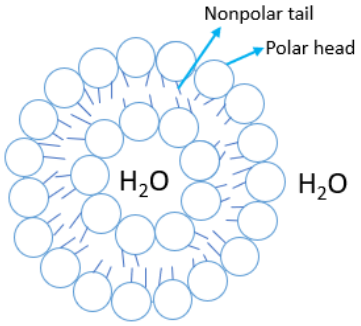

Fig. 2: Liposome (designed by authors)

Solid Lipid Nanoparticle (SLN) is a nano-delivery system that is an alternative to liposomes. SLN consists of 0.1-30% solid fat dispersed in the aqueous phase, to which 0.5-5% surfactant is added as a stabilizer [38]. The fats used are divided based on their structure: fatty acids, esters, fatty alcohols, and triglycerides [39]. An example of using SLN in isolates is piperine, where piperine is insoluble in water [40]. Piperine is a biological component isolated from the Piper nigrum plant [41]. SLN piperine was prepared by emulsification-solvent diffusion method, where piperine, glycerol monostearate, and epikuron 200 were mixed in demineralized water, then emulsified with benzyl alcohol (containing tween 80). The results of the piperine release test in the brains of the test animals showed that the piperine SLN had Cmax: 121±6.78 ng/g and Tmax: 60±9.8 min, while the results of pure piperine were Cmax: 51±9.34 ng/g and Tmax: 180±10.3. The increase in Cmax is doubled, and Tmax is achieved much faster [42].

Nanomicelles are nanosystems consisting of amphiphilic colloidal structures measuring 5-100 nm. There are two parts of this micelle based on their affinity in water: a hydrophilic and a hydrophobic part [43]. Nanomicell will work as a protective shell of the drug from the body's environment, thereby increasing the bioavailability of the drug and reducing side effects [44]. An example of nano micelles is in water-insoluble quercetin [45]. Quercetin is abundant in broccoli, oranges, apples, green tea, and onions [46]. The preparation of quercetin nano micelles used the thin-film hydration method, in which quercetin with polymer (10 mmol) was dissolved in ethanol

and evaporated with a rotary evaporator under low pressure. The test results showed an increase in the solubility of quercetin in the form of nano micelles, which increased up to three times compared to pure quercetin [47].

PLGA (Poly lactic-co-glycolic acid) is the most commonly used polymer in developing nanoparticles because it can be degraded in the body. PLGA will be hydrolyzed into lactic acid and glycolic acid, which are metabolized through the Krebs cycle to carbon dioxide and water [48]. The FDA has approved PLGA for use in the human nanomedicine field [49]. An example of using PLGA nanoparticles is in quercetin, where PLGA-quercetin nanoparticles are made using the solvent evaporation method. The test results showed that the release profile of quercetin bound to PLGA nanoparticles reached 65%, while pure quercetin did not reach 40% [50].

Solid dispersion

A solid dispersion is a mixture of solid materials consisting of at least two different components with different properties, which are hydrophilic and hydrophobic [51]. The solid dispersion is applied to a substance having poor solubility, and then the substance is dispersed in a solid polymer [52, 53]. Solid dispersion is one method widely used to increase the solubility of a substance [54].

An example of solid dispersions is in curcumin, which is made using soluplus polymer and solvent evaporation preparation. Firstly, curcumin and soluplus were dissolved in acetone. Then acetone was evaporated. This solid dispersion of curcumin has a dissolution efficiency of 94.84±2.54%, while pure curcumin does not reach 60% [55]. In addition to soluplus, eudragit EPO polymer can be used to form solid dispersions with curcumin. Make this solid dispersion using a spray dryer with acetone solvent. The dissolution results showed that the release of curcumin in solid dispersion outperformed the release rate of pure curcumin, where the release of solid dispersion reached 40% at pH 6.8 while pure curcumin was below 20% [56]. PEG and HPMCAS polymers have also been shown to increase the release and solubility of curcumin [57, 58].

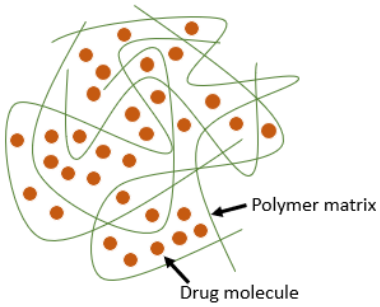

Fig. 3: Ideal solid dispersion (designed by authors)

Another example is the formation of solid dispersions of piperine using PEG, sorbitol, and PVP. Solid dispersion preparation by solvent evaporation method where piperine is dissolved in ethanol. The release of pure piperine in the 2nd hour of the dissolution test was 4.4%, while the release in the form of solid dispersion reached 70% (Sorbitol), 76% (PEG), and 89% (PVP) [59]. In other isolates, such as quercetin and andrographolide, solid dispersion was able to increase the release in the dissolution test [60-62]. Then in myricetin, solid dispersion increases solubility in water [63].

Complexion

The complex is an intermolecular combination of substrate and ligand due to covalent or non-covalent bonds (hydrogen bonds, van der Waals forces, electrostatic bonds, and dipole-dipole forces). The most frequently used complexing agent is cyclodextrin [64]. Complexation can increase the solubility of substances in water and the speed of dissolution. There are several types of complexes, namely coordination complexes (metal complexes), molecular complexes, and inclusion complexes [65].

A coordination/metal complex consists of a central metal ion/atom bonded to a ligand. If derived from natural materials, usually, these metals bind to ligands involved in photosynthesis or metabolism [66]. Some metals that can form complexes are Fe2+, Fe3+, Co2+, Co3+, Cu2+, Zn2+, Ag+, and Pt4+, which are transition metal ions. Covalent bonds bind the metal to the ligand (neutral or anionic) [64]. Examples of the application of coordination complexes are curcumin and quercetin, which bind to magnesium (Mg) and calcium (Ca). In this complex, each metal molecule contains two molecules of curcumin or quercetin. The solubility of curcumin and quercetin in the complex form increases, whereas in the pure state, the solubility in water is 0.15 mg/l (curcumin) and 0.21 mg/l (quercetin) to 1.442 mg/ml (Mg-curcumin), 1.508 mg/l. ml (Ca-curcumin), 1.696 (Mg-quercetin), and 1.808 mg/ml (Ca-quercetin) [67].

Molecular complexes consist of substrates and ligands bound by non-covalent bonds that tend to be weak [64]. Examples of non-covalent bonds that bind substrates and ligands are hydrogen bonds, electrostatic forces, van der Waals forces, and hydrophobic forces [65]. An example of molecular complexes is apigenin, where apigenin is bound to phospholipids by hydrogen bonds. These apigenin and phospholipid complexes are more commonly referred to as pyrosomes, increasing their water solubility up to 35 times compared to pure apigenin. The solubility of phytosomes in water was 22.80±1.40 g/ml, while pure apigenin was only 0.62±0.88 g/ml due to a decrease in the crystalline level of apigenin which turns into a partially amorphous form [68].

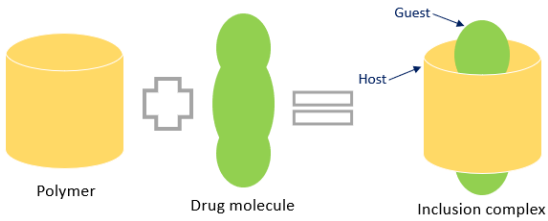

Fig. 4: Inclusion complex (designed by authors)

The inclusion complex consists of two or more molecules, one acting as a "host" and the other as a "guest". Hydrophobic molecules will stick to the gaps of molecules that act as hosts and are hydrophilic [69]. An example of the use of inclusion complexes is in naringenin. Naringenin belongs to the flavonoid group found in oranges or tomatoes. Naringenin is insoluble in water and soluble in alcohol [70]. The formation of the naringenin inclusion complex with cyclodextrin increased its solubility in water, where the solubility of pure naringenin was 41.81 g/ml, while in the form of the inclusion complex, it was 74.28 g/ml. The increase in solubility was due to the inclusion complex structure protecting the hydrophobic moiety of naringenin [71].

A further example is piperine made into inclusion complexes with HPMC and-cyclodextrin increasing release in the dissolution test. The results showed that the piperine release in 60 min reached 95.78%, while pure piperine was only 22.04% [72]. Using ethylenediamine cyclodextrin in piperine also increased the dissolution release, where the release of pure piperine in the 5th minute was 35%, and the 60th min was 40%, while the inclusion complex in the 5th minute had reached 70% and at the-60 reaches 100% [73]. In other isolates, namely curcumin, quercetin and myricetin, the formation of inclusion complexes with cyclodextrin also increased the release in the dissolution test [74-76].

Microencapsulation

Microencapsulation by spray drying is an encapsulation technology that has been widely used and allows the active component to enter into a sturdy, spherical, semipermeable polymer matrix called microcapsules [77]. Microencapsulation consists of tiny particles or droplets surrounded by a film or polymer layer to protect them from the environment and regulate their release [78]. Microencapsulation is also used to mask bitter tastes, increase solubility [79], and prevent drug degradation [80]. In addition, using micro-

encapsulation can increase its bioavailability during oral administration. The maximum concentration of encapsulated curcumin in eudragit was 478.45 ng/ml in blood plasma, while pure curcumin was only 89.67 ng/ml [81].

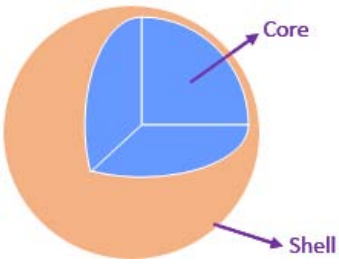

Fig. 5: Microencapsulation (designed by authors)

Solubility enhancement polymer

Cyclodextrin

Cyclodextrins (SD) are synthesized from starch by enzymatic reactions into cyclic oligosaccharides. Cyclodextrins are non-toxic, biodegradable and natural [82]. Cyclodextrins consist of some glucopyranose monomers attached to 1,4-glycoside bonds [83]. Unmodified cyclodextrins have poor solubility and cannot bind strongly to drug molecules. Meanwhile, cyclodextrin derivatives have good solubility, are stable, and can bind to drug molecules [82]. Some examples of cyclodextrin derivatives are-SD,-SD,-SD, Hydroxypropyl-α-SD (HP-α-SD), Hydroxypropyl-β-SD (HP-ß-SD), Hydroxypropyl-γ-SD (HP-γ-SD), Sulphobutylether-SD, 2-Hydroxypropyl-γ-SD, ethylenediamine cyclodextrin (E-ß-SD), and methylated-β-SD [84]. Cyclodextrins were used to increase the solubility of curcumin solid dispersions [85] and curcumin inclusion complexes [86-87].

Table 4: Cyclodextrin use in isolate

Type	Isolate	Method	Reference
HP-ß-SD	Curcumin	Solid Dispersion	[85]
		Inclusion Complex	[86-88]
	Myricetin	Inclusion Complex	[76]
ß-SD	Piperine	Inclusion Complex	[72]
	Naringenin	Inclusion Complex	[71]
	Quercetin	Inclusion Complex	[75]
E-ß-SD	Piperine	Inclusion Complex	[73]
HP-α-SD	Curcumin	Inclusion Complex	[88]
HP-γ-SD	Curcumin	Inclusion Complex	[88]

Polyvinylpyrrolidone

Polyvinylpyrrolidone (PVP) is a polymer consisting of a linear group of 1-vinyl-2-pyrrolidone. This polymer has a carbon chain containing an amide group on the side chain and a poly-N-vinyl amide structure. PVP is non-toxic, biocompatible, inert, and stable [89]. PVP has good solubility in water and solvents with polar properties [90]. PVP can envelop hydrophilic and lipophilic drugs, making them suitable for use in the modification of drug delivery [91]. PVP increases solubility through solid dispersion systems in quercetin, curcumin, and rutin [35].

Table 5: PVP use in isolate

Type	Isolate	Method	Reference
PVP-K30	Curcumin	Solid Dispersion	[35]
	Quercetin	Solid Dispersion	[35]
	Rutin	Solid Dispersion	[35]
	Piperine	Solid Dispersion	[59]
PVP	Myricetin	Solid Dispersion	[92]
	Daidzein	Solid Dispersion	[93]

Hydroxy propyl methyl cellulose

Hydroxy Propyl Methyl Cellulose (HPMC) is cellulose obtained by treating alkaline cellulose with chloromethane and propylene oxide. HPMC is a powder soluble in cold water, odourless, tasteless, and white [94]. HPMC can be stable in the pH range of 3–11 and can form solid dispersions to stabilize amorphous substances. According to the FDA and EMA, HPMC has also been classified as a safe excipient [95]. HPMC was used to increase the solubility of the piperine inclusion complex [72] and the solid dispersion of quercetin [62].

Table 6: HPMC use in isolate

Type	Isolate	Method	Reference
HPMC	Piperine	Inclusion Complex	[72]
	Quercetin	Solid Dispersion	[62]
	Myricetin	Solid Dispersion	[92]
	Curcumine	Solid Dispersion	[96]

Polyethylene glycol

Polyethylene glycol (PEG) is a hydrophilic polymer synthesized from ethylene oxide. This polymer consists of repeating O-CH2-CH2 units [97] and has good solubility in water, ethanol, acetonitrile, benzene, and dichloromethane. PEG has many forms, such as forked, star, and comb. PEG can bind to drug molecules, which will prevent drug molecules from binding to proteins. PEG binding to drug molecules is called PEGylation [98]. PEG increased the solubility of luteolin solid dispersions [26] and quercetin solid dispersions [99].

Table 7: PEG use in isolate

Type	Isolate	Method	Reference
PEG 4000	Luteolin	Solid Dispersion	[26]
	Curcumin	Solid Dispersion	[58]
PEG 6000	Curcumin	Solid Dispersion	[58]
PEG 8000	Quercetin	Solid Dispersion	[99]
PEG 20000	Piperine	Solid Dispersion	[59]

Chitosan

Chitosan is a random copolymer resulting from chitin deacetylation, formed from D-glucosamine and N-acetyl-D-glucosamine linked to-1,4 glycosidic [100]. Chitosan is a natural cationic polysaccharide and is non-toxic [101]. The solubility of chitosan depends on molecular weight, degree of acetylation, pH, temperature, and crystallinity [102]. There is also chitosan which is modified by adding a hydrophilic group so that it has good solubility in water. Synthesis of water-soluble chitosan can be done by breaking the polymer chain through an enzymatic hydrolysis process to reduce the molecular weight of chitosan and increase the solubility of chitosan. In addition, there is a graft polymerization method in which chitosan polymer is added with a water-soluble dicyandiamide branch [103]. Chitosan was used to increase the curcumin nano complexes' release rate [104].

Eudragit

Eudragit is a polymer that has many types with different solubility properties. Eudragit is a synthetic polymethacrylates polymer with anionic, cationic, and nonionic properties consisting of a combination of dimethylaminoethyl methacrylates, methacrylic acid, and methacrylic acid esters with different ratios. Eudragit is stable, has good compressibility, and regulates drug release based on environmental pH [105]. Eudragit was used to increase the solubility of curcumin in solid dispersion [56] and microencapsulation [81].

PLGA

Poly(lactic-co-glycolic acid), abbreviated as PLGA, is a synthetic polymer that can be degraded naturally, biocompatible, and non-toxic. PLGA was synthesized from lactide and glycolide, combined at a temperature of 160–190oC under vacuum with a stannous octoate catalyst. These polymers have characteristics that depend on the percentage of lactide and glycolide, such as crystal shape, density, and glass transition temperature [106]. PLGA was used in the formation of quercetin nanoparticles in order to increase their dissolution [107].

Soluplus

Soluplus is another name for the polymer polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer, which is an amphiphilic polymer with excellent solubility, so it is used in increasing the solubility of drugs. Good solubility because soluplus has many hydroxyl groups [108]. Soluplus increased the solubility of curcumin solid dispersions [55].

CONCLUSION

Based on this literature review, it can be concluded that the solubility problem of isolates can be overcome by applying the isolate modification method and combining isolates with polymers. Further research is needed to assess the effectiveness of these methods and polymers in increasing the solubility of isolates.

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AUTHORS CONTRIBUTIONS

FDRN: conception, design, and drafting of the article. S and AYC: participated in intellectual discussions and critical revision of the article. All authors approved the final version of the manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest in this article.

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