



Review on the effect of Opium on the Cardiovascular System

Dhananjay Kumar Bharkher^{1*}, Md. Zulphakar Ali², Himani Tiwari³ and Kaushal Kishor Chandrul⁴

1, Student of B. Pharm. 4th Year; 2, Assistant Professor; 3, HOD; 4, Principal

Department of Pharmacy, Mewar University, Gangrar Chittorgarh, (R.J.) - India

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Abstract

Opioids have the best price of illicit drug intake after hashish worldwide. Opium, after tobacco, continues to be the maximum generally abused substance with inside the Middle East. In addition to the convenience of availability, one cause for the excessive intake of opium in Asian international locations is probably a conventional notion amongst Eastern human beings or even scientific team of workers that opium may also have ameliorating consequences on cardiovascular diseases (CVDs) in addition to diabetes mellitus, hypertension, and dyslipidemia. Over the final decade, many studies were achieved on human beings and animals to assess the interaction among opium intake and solid coronary artery disease, acute coronary syndromes, and atherosclerosis. In this review, we finish that opium intake must be taken into consideration a chance thing for CVDs. Healthy individuals, as nicely as cardiac and diabetic patients, must be knowledgeable and knowledgeable approximately the dangerous consequences of opium intake on cardiovascular and different persistent diseases.

Key words: Opium, Cardiovascular, Drugs

Introduction

Papaver somniferum L. is among the oldest medicinal plants, and the dried latex of its poppy, opium, has been used for medicinal or leisure functions conventionally.¹ Opioids have the highest fee of illicit drug intake after hashish worldwide. In 2017, the United Nations Office on Drugs and Crimes suggested that 29 million persons, 50% better than estimates, had used opiates withinside the previous yr globally.² Notably, opium, after tobacco, continues to be the maximum usually abused substance withinside the Middle East.^{three} One of the motives for the excessive use of opium on this location is probably the convenience of get entry to and additionally the area withinside the predominant pathway of the opium transit as the principle opium-generating

nations which includes Afghanistan, and to a lesser extent, Myanmar, and Laos are positioned on this region. In addition to the benefit of availability, any other motive is probably a conventional perception amongst Eastern humans or even scientific team of workers that opium may also have ameliorating outcomes on cardiovascular diseases (CVDs) in addition to diabetes mellitus, hypertension, and dyslipidemia.^{4e9} Over the remaining decade, many research were executed on people and animals to assess the impact of opium consumption on blood lipid and glucose profiles, and additionally on CVDs.

***Corresponding Author**

In 2013, we posted the primary assessment article at the cardio-metabolic outcomes of opium consumption.¹ In this assessment, we aimed to acquire and combine the latest proof with our preceding expertise to make clear the outcomes of opium on CVDs and its underlying mechanisms.

Pharmacotoxicology

The phrase opium (lachryma papaveris, Teriak) is derived from the Greek call for juice; a milky juice extracted with the aid of using incising the unripe capsules (poppy) of *Papaver somniferum* L. After being uncovered to air, it turns into a brown, sticky, or crumbly substance. It is a complex cocktail of materials that, similarly to water, includes extra than forty alkaloids¹¹ and over 70 components.¹² Only 5 of those alkaloids account for certainly all the quantitative alkaloid content material of opium (Fig. 1), inclusive of morphine (8e17% through weight), noscapine (1e10%), papaverine (0.5e1.5%), codeine (0.7e5%), and thebaine (approximately 0.2%). eleven Morphine and codeine are powerful ache relievers thru the activation of the m (mu) opioid receptor. However, they also are abused for leisure functions due to the fact the activation of the m receptor reasons euphoria and drowsiness. thirteen Noscapine (previously referred to as narcotine) is an antitussive agent.¹⁴ Papaverine has no morphine-like actions, however because it relaxes clean muscles, it is usually used for the prevention and remedy of vasospastic illnesses along with the spasm of coronary artery skip grafts. eleven, 14 Opium is used thru special routes.

It maybe ingested orally or smoked after direct heating with burning charcoal in specialized gadgets along with an opium pipe (Vafour). In every other route (Sikh Sang), a stick is heated and the opium is placed on the heated stick with a hairpin, after which the smoke is inhaled.¹⁵ When opium is ingested, the onset of motion is delayed.¹ This is while, within the case of opium smoking, morphine reaches the mind inside seconds due to the fast absorption of its vapor throughout the pulmonary capillaries into the bloodstream. Therefore, the onset of motion is an awful lot extra fast and extreme after smoking, however the period of motion is longer after oral consumption due to the fact the absorption from the intestine, despite the fact that slower, keeps

over an extended period

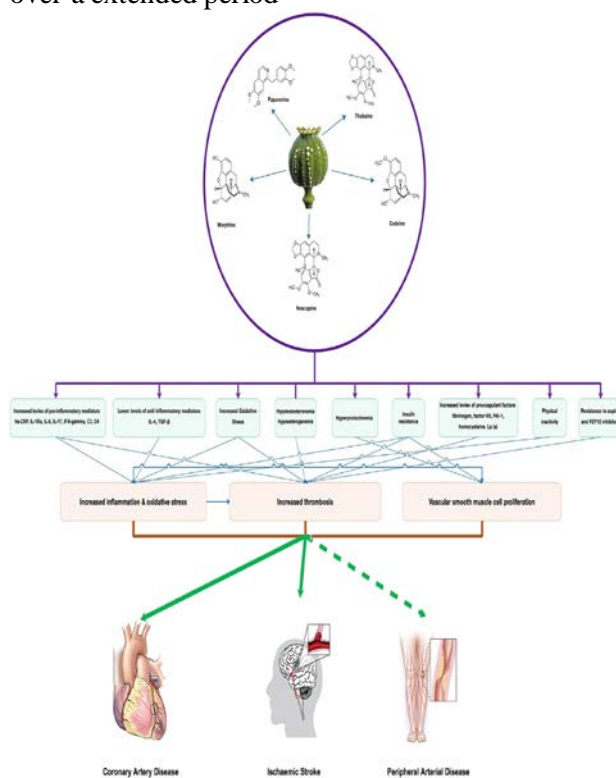


Fig. 1: Central illustration: Chemical structure of five main alkaloids of opium (*Papaver somniferum* L.) and the potential mechanisms of the harmful effects of opium consumption on coronary artery disease, ischemic stroke, and peripheral arterial disease. hs-CRP, high sensitivity C-reactive protein; IL, interleukin; IL-1Ra, interleukin-1 receptor antagonist; IFN-g, interferon-g; Lp (a), lipoprotein (a); PAI-1, plasminogen activator inhibitor-1; TGF-b, transforming growth factor-b.

Stable coronary artery disease

Clinical research

In the first actual look at the affiliation among opiates and coronary artery disease (CAD), investigators as compared ninety eight decedents with methadone or opiate (M/O) of their blood on the time of post-mortem and ninety seven decedents with out M/O, and located a decreased severity of CAD many of the former sixteen. Although they concluded that long-time period opiate publicity would possibly mitigate CAD severity and its fatal consequences, they referred to as for warning at the same time as decoding their

outcomes primarily based totally on numerous limitations, which includes a loss of information at the decedents' smoking histories, lipid profiles, and lifestyles. sixteen Subsequently, majority of research besides few located that opium intake is related to greater excessive and extensive involvements of coronary arteries, even after modifications for viable confounders (Table 1).^{10,17e22} A cross-sectional take a look at determined no affiliation among opium intake with the aid of using any route and ischemic coronary heart diseases.²³ However, the authors referred to as for warning at the same time as decoding their outcomes because the opium dosage, the suggest period of opium intake, and the purity of opium had been now no longer assessed of their take a look at (Table 1).²³ A latest meta-analysis confirmed that opium intake turned into related to a extensively more threat of CAD (odds ratio [OR]: 2.77, 95% confidence interval [CI]: 2.04 to 3.75).²⁴ Besides research comparing the affiliation among opium intake and the presence, severity, and extension of stable CAD, opium abuse has been validated to be associated to coronary microvascular dysfunction. Opium abuse turned into an unbiased predictor of coronary microvascular dysfunction (OR: 3.575, 95% CI: 1.418 to 9.016; $p = 0.0069$) in a cross-sectional take a look at on sufferers with documented microvascular dysfunction.²⁵ Further, every other latest take a look at found out that opium intake turned into an unbiased threat thing for CAD and coronary artery ectasia.

Animal studies

It has been verified that opium dependancy has aggravating results at the development of atherosclerosis within the aorta of hypercholesterolemic rabbits.^{four} However, this atherogenic impact was confined to hypercholesterolemic as opposed to normocholesterolemic conditions.^{four} Concordantly, 4 weeks of opium smoking increased the atherogenic index in hypercholesterolemic rabbits and now no longer in normocholesterolemic ones.²⁷ Another look at confirmed that despite the attenuation of myocardial necrosis in rabbits with myocardial ischemia, opium publicity annoyed ischemia susceptibility, myocardial congestion, and hemorrhage.²⁸ In summary, there's steady proof

helping the affiliation among opium intake and solid CAD.

Acute coronary syndromes

Although there's an settlement amongst contemporary research that opium intake is undoubtedly related to the presence and severity of CAD, there's controversy approximately the affiliation between opium intake and acute myocardial infarction (MI).²⁹ Some investigations have suggested unfavorable effects,^{30,31} whilst others have proven impartial effects (Table 2).³² Despite the talk concerning the affiliation between opium intake and the occurrence of acute MI, there's an settlement concerning the effect of opium intake at the in-hospital and mid-time period effects of acute MI. Research has proven that opium use isn't correlated with multiplied rates of post-MI mortality, morbidity, and readmission.^{6,31,33e35} Nevertheless, some investigators have suggested remarkably longer health facility lengths of stay,³⁵ better readmission rates,³⁶ and borderline extensively better in-hospital mortality rates (11.5% vs. 5.9%; $p = 0.072$)³⁶ in opium-established sufferers with acute MI in preference to non-opium users (Table 2). Altogether, now no longer handiest there no proof for assisting a reduced hazard of acute MI or a good post-MI final results in opium-established sufferers however additionally it can be related to more post-MI complications. Summary of studies evaluating the association of opium consumption with acute coronary syndrome and its outcomes.

Clinical research on sufferers present process revascularization

Some research on coronary artery pass grafting surgical treatment (CABG) applicants have confirmed that opium intake is now no longer correlated with multiplied in-hospital mortality rates, postoperative hardship rates, or in-hospital lengths of stay.^{37e40} However, others have proven that opium use is immediately correlated with intra- and post-operative bleeding,^{forty one} readmission,³⁸ and longer in-hospital lengths of stay.^{forty} Recently, we studied 28,691 sufferers who underwent CABG for a mean of fifty six months to assess the results of opium intake and cessation at the long-time period results of those sufferers.^{forty two} In this cohort, 3636 sufferers endured opium intake

after surgical treatment, even as 1436 sufferers stopped opium use. After modifications for viable confounders, we discovered that in assessment with the in no way customers of opium, chronic opium intake after CABG changed into related to multiplied 5-12 months all cause mortality (danger ratio [HR]: 1.28, 95% CI: 1.06 to 1.54; $p = 0.009$) and 5-12 months important damaging cardiac events (MACE) (HR: 1.25, 95% CI: 1.13 to 1.40; $P < 0.0001$). Still, individuals who quitted opium use after surgical treatment have been now no longer at an multiplied chance of mortality (HR: 1.09, 95% CI: 0.83 to 1.43; $p = 0.514$) or MACE (HR: 1.03, 95% CI: 0.88 to 1.21; $p = 0.645$) at 5 years in comparison with the in no way customers of opium. In a retrospective cohort study, opium intake changed into now no longer related to 12-month MACE amongst male sufferers after optional percutaneous coronary interventions, and not one of the additives of MACE, inclusive of goal vessel revascularization, goal lesion revascularization, CABG, and non-deadly MI, changed into unique among opium customers and non-customers. Nonetheless, it have to be stated that even as age is an vital predictor of MACE, specially mortality, the authors did now no longer make modifications for the confounding impact of age on MACE notwithstanding the extensively lower age of the opium customers via way of means of assessment with the non-customers (55.7 as opposed to 58.4 years, respectively; $p < 0.001$). This bias may probably underestimate MACE within the opium consumer group. Altogether, it seems that opium intake now no longer best has no ameliorating impact on sufferers present process coronary revascularization however additionally can also additionally have dangerous results on mid-time period and longer outcomes.

Stroke

There are scarce reviews approximately the correlation among opium and stroke (Table 3). In a case control look at, opium abuse was independently related to ischemic stroke. Other studies have established that opium dependancy is related to expanded intima-media thickness, greater atherosclerotic plaques, and a

extra pulsatility index and imply go with the drift pace of the middle cerebral artery, which might be the markers of cerebral atherosclerosis.⁴⁵⁻⁴⁷ In a look at on male CABG candidates, there has been no distinction in the superiority of enormous carotid artery stenosis among opium-addicted and non-addicted sufferers. forty eight Nevertheless, there's a enormous bias on this look at because the authors said a better incidence of diabetes (17% as opposed to 11.4%) and hypertension (88.6% as opposed to 11.4%) in addition to a decrease incidence of smoking (27.1% as opposed to 65.5%) within the non-addicted sufferers than within the opium addicted ones, respectively. Indeed, no end may be drawn approximately the affiliation among opium intake and carotid stenosis with out adjusting for such essential confounding factors (Table 3).

forty eight In summary, the presently constrained proof shows the destructive outcomes of opium on cerebral atherosclerosis and hemodynamic abnormalities, and its affiliation with ischemic stroke. Nonetheless, in addition research are had to elucidate the association among opium intake and stroke.

Peripheral arterial disorder

Despite numerous research assessing the connection among opium intake and CAD, there may be confined facts concerning the affiliation among opium intake and peripheral arterial disorder. In a take a look at on sufferers with peripheral arterial disorder who underwent decrease extremity vascular reconstruction surgery, investigators determined that the patency price changed into extensively decrease in opium customers than non-customers (32% as opposed to 67%, respectively). forty nine However, the authors did not modify this locating for potential confounders. forty nine Future well-designed research have to elucidate the actual position of opium intake in peripheral arterial disorder.

Heart failure

The affiliation among opium intake and left ventricular systolic disorder has been evaluated in lots of latest research. The contemporary proof means that opium intake is now no longer related to a reduced practical elegance.^{23,33,34,37-39,50-52} Nevertheless, there are conflicting consequences concerning the affiliation among opium intake and the left

ventricular ejection fraction (LVEF). Some research has proven that opium customers, with or without CAD, are much more likely to have decreased LVEF than nonusers,^{50,51} fifty three, fifty four whilst others have observed an impartial impact on this regard.^{10,20,23,31,33e35,37-39,43,52}, fifty five A latest meta-evaluation confirmed that opium use changed into related to extensively decrease LVEF in opium customers who have been applicants for CABG (mean variations \pm 2.15, 95% CI: 3.31 to 1).²⁴ However, this statistically good sized distinction of 2%, perhaps of no or minimum medical importance. Moreover, this correlation did now no longer attain statistical importance in different subgroups of sufferers with CAD (mean variations \pm 0.29, CI: 0.57 to 1.14).²⁴ Taken these types of strains of proof together, we might also additionally finish that opium intake has impartial outcomes at the LVEF and practical elegance of people with coronary heart failure.

Cardiac arrhythmias

Studies have verified that opium use is related to a better occurrence of ventricular arrhythmias within the post-MI course, even after changes for confounders,⁵² fifty six whilst every other take a look at confirmed an impartial impact on this regard.³⁴ Whereas a take a look at confirmed that opium dependancy changed into related with better post-CABG arrhythmias, fifty three every other take a look at observed defensive outcomes for opium use in phrases of post-CABG atrial traumatic inflammation. fifty seven Despite those controversies in medical research, animal studies²⁷, fifty eight have always indicated a proarrhythmic impact for opium.²⁹ Future well-designed potential medical research have to elucidate the precise position of opium intake in inducing or stopping cardiac arrhythmias.

Interactions with cardio-vascular tablets

The contemporary proof suggests that opiates can intrude with cardiovascular medicinal drugs via changes of their pharmacokinetics or pharmacodynamics. fifty nine In a massive take a look at, an evaluation of prescriptions for sufferers with non-valvular atrial traumatic inflammation who have been below remedy with warfarin and had a solid international normalized ratio (INR) indicated that the intake of opiates, consisting of herbal opium,

buprenorphine, and tramadol, changed into related to an extended INR in those sufferers, which would possibly suggest a clinically crucial interplay.⁶⁰ Furthermore, it's been proven that the concomitant use of opium and digoxin might also additionally boom the danger of digoxin toxicity.⁶¹ Another clinically applicable interplay of opium is with antiplatelets. Research has proven that the management of opium, inclusive of opium, methadone, and morphine attenuates the antiplatelet moves of aspirin, sixty two ticagrelor,^{63e65} prasugrel,⁶⁴, sixty six and clopidogrel.⁶⁷, sixty eight This listing of doubtlessly lethal interactions among opium and cardiovascular tablets shows that cardiologists and cardiac surgeons act carefully while prescribing antiplatelets, digoxin, and warfarin for an opium-abusing patients.

Temporal dating among opium intake and cardiovascular diseases

Although the medical research at the affiliation among opium intake, and CAD and stroke have set up a systematic base within the proof pyramid, there are not unusual place obstacles of their methodologies that name for warning in decoding their consequences. First, all of those research have case control or cross-sectional designs. Some sufferers with CAD or stroke possibly begin the use of opium due to their signs or their ideals approximately the useful outcomes of opium use on CVDs following the improvement of their diseases. Hence, whilst we have a look at a better incidence of opium intake amongst sufferers with CVDs than healthful people, we can not make a causal interpretation due to the fact the temporal courting among opium intake and CVDs can't be decided in those research. Another problem is the possible occurrence-prevalence bias, which ought to be taken into consideration in cross sectional and case control research. If opium intake affects the survival of sufferers with ischemic coronary heart diseases, then the outcomes of cross-sectional research with popular instead of incident instances might be biased. Community-primarily based totally cohort research can conquer those boundaries and assist to make causal interpretations of the connection among opium and CVDs. With the

growing use of opioids for persistent non-cancer pain, a huge nested case control examine established that using opioids become related to an expanded danger of MI (OR: 1.28, ninety five% CI: 1.19 to 1.37).

In our opinion, the maximum supportive proof for a possible dangerous function of opium intake in CVDs got here from the Golestan Cohort Study.⁷⁰ The Golestan Cohort Study recruited 50, half human beings elderly 40e75 years from January 2004 to June 2008 from Golestan Province, placed in North Iran. As distinctive exposure data, a scientific follow-up approach, and the ascertainment of the purpose of demise have been available, the investigators evaluated the affiliation among opium intake and all-purpose mortality and predominant categories, consisting of circulatory reasons for mortality after a mean follow-up of 4.7 years. The adjusted HR for all-purpose mortality related to ever use of opium become 1.86 (ninety five% CI: 1.61 to 2.06).

They additionally determined that opium customers have been at an expanded danger of demise from ischemic coronary heart diseases (adjusted HR: 1.90; ninety five% CI: 1.57 to 2.29). Moreover, after apart from the men and women who started opium use after receiving a analysis of predominant illnesses, namely ischemic coronary heart diseases, cerebrovascular occasions, diabetes mellitus, and hypertension, they observed a dose response affiliation among the period of opium use and cardiovascular in addition to all cause mortality. Unlike preceding cross-sectional and case control research, the Golestan Cohort Study become now no longer problem to the aforementioned predominant boundaries and, therefore, it's far affordable to finish causality primarily based totally on its findings.

Association among opium intake and cardiovascular diseases: impartial or confounded through smoking?

Cigarette smoking is one of the predominant danger elements for CVDs. It has been proven in all preceding research that opium abusers smoke cigarettes greater frequently.^{10,36,48} Thus, it isn't always clean whether or not the affiliation among opium intake and CVDs is a dependent affiliation confounded through smoking or opium intake is an impartial danger thing for

CVDs. Numerous research have attempted to solution this question. In a propensity rating matched analysis, the examine found out that diabetic opium customers had greater intense CAD than matched diabetic non-customers.^{10A} A huge cross-sectional examine indicated a better occurrence of CAD in opium customers than non-customers, even after the exclusion of cigarette smokers (Table 1).¹⁷ In a nested case control examine, opium dependancy become an impartial danger thing for CAD among non-smokers, whilst this affiliation become now no longer great in cigarette smokers.²⁰ Hence, we are able to finish that the courting among opium intake and CVDs is impartial.

Why ought to opium intake be related to cardiovascular diseases?

Current understanding is scarce approximately the results of opium on blood glucose, dyslipidemia, and hypertension. seventy one Although animal research show the dangerous results of opium at the aforementioned danger elements, there are a few discrepancies in medical research. seventy one Thus, it requires destiny well-designed medical research to cope with this gap of understanding. Here, we are able to attention on different danger elements and novel mechanisms of opium results on CVD.

Studies have established that opium exerts its dangerous results on CVDs thru expanded infection and oxidative pressure, expanded thrombosis, and vascular clean mobileular hyperplasia (Fig. 1). Although there's a complicated courting, we in brief speak those interwoven elements here. Recent research have more and more said that opium addicts have multiplied stages of pro-inflammatory mediators^{15,72e76} and decrease stages of anti-inflammatory cytokines.^{74,75} On the opposite hand, it's been proven in numerous research that morphine and heroin set off systemic oxidative pressure and decrease the full antioxidant potential impartial of cigarette smoking.

Hypotestosteronemia and hypoestrogenemia in opium addicts⁷⁸ can also additionally bring about CVDs thru all the aforementioned mechanisms. These hormonal imbalances are related to expanded stages of procoagulant elements and insulin resistance.^{79e86} Studies

have additionally established that opium-addicted individuals have remarkably better stages of procoagulant elements than nonaddicted individuals.^{15,87e90} Additionally, studies have validated a country of insulin resistance, much like sufferers with kind 2 diabetes mellitus, ninety one which reasons CVDs.^{79e86,89,92,ninetythree} Opium abusers have hyperprolactinemia,^{78,ninetyfour} which hinders proliferation of vascular lean muscle cells and CVDs.^{ninetyfive} Another mechanism is the discount of bodily pastime because of the depressant results of opium at the significant anxious system, ninety six that's related to an expanded danger of CVDs.^{97e100}

Last however not least, is the resistance to aspirin and P2Y₁₂ inhibitors in opium customers. We formerly mentioned that opium intake blunts the pharmacological results of aspirin,⁶² ticagrelor,^{63e65} prasugrel,⁶⁴ sixty six and clopidogrel.⁶⁷, sixty eight These findings can also additionally render opium customers with preceding CVDs greater prone to acute thrombotic occasions and is probably a singular justification for better dangers of MI and stroke in those sufferers.

Strategies for the remedy of opioid dependence

For the a success remedy of opioid dependence, we ought to rent pharmacological interventions except psychosocial supportive measures. There are techniques towards pharmacological remedy: 1) opioid agonist preservation remedy with long-performing opioids together with methadone or buprenorphine, which is the best and the favored method, and 2) detoxification, observed through remedy with long-performing opioid antagonists together with naltrexone, to save you relapses. Other than those medications, alpha-2 adrenergic agonists together with clonidine for the remedy of opioid withdrawal and naloxone for the remedy of opioid overdose ought to be available.

Conclusion

People have used opium for decades now no longer handiest as a habit, however primarily based totally on their conventional ideals approximately its useful results on diabetes mellitus, dyslipidemia, hypertension, and CVDs. Considering the modern-day proof, opium now no longer handiest has no ameliorating impact on

CVDs, however the medical, animal, and potential cohort research continuously suggest that opium intake is associated with CVDs and cardiovascular mortality. Moreover, the rapidly developing organic motives for a causal courting among opium intake and CVDs underscore the caution that opium intake ought to be taken into consideration a danger thing for CVDs. Unfortunately, fake ideals concerning the useful results of opium are common, and it's far the duty of fitness professionals¹⁰² and fitness government to warfare in opposition to those fake beliefs. Healthy people, in addition to cardiac and diabetic patients, need to be informed and knowledgeable approximately the dangerous results of opium consumption on cardiovascular and different continual diseases

Highlight

- There is regular proof helping the affiliation among opium intake and strong coronary artery disease.
- Persistent opium intake after coronary artery pass grafting surgical treatment is related to increased long-time period dangers of mortality and primary destructive cardiac events.
- The presently confined proof indicates the detrimental outcomes of opium on cerebral atherosclerosis, and hemodynamic abnormalities and its affiliation with ischemic stroke.
- A dose response affiliation exists among the duration of opium use and all-motive and cardiovascular mortality.
- Opium intake must be taken into consideration a chance factor for cardiovascular diseases.
- Physicians must ward off fake ideals approximately the useful outcomes of opium.

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