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Review Article

The Clinical Pharmacology of Milk-Drug Interactions: From Pharmacokinetic Principles to Recent Therapeutic Recommendations

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ABSTRACT

Milk consumption can significantly alter the pharmacokinetic and pharmacodynamic properties of drugs, impacting their therapeutic efficacy and safety. These interactions primarily affect orally administered medications through several key mechanisms. This review aims to systematically summarize the pharmacokinetic and pharmacodynamic mechanisms of milk-drug interactions, analyze their clinical implications across diverse populations, and provide practical recommendations to optimize therapeutic efficacy and safety. A major factor is milk's high calcium content, which can chelate with drugs like tetracyclines and fluoroquinolones, forming insoluble complexes that may reduce drug bioavailability by as much as 50–60%. Furthermore, milk proteins such as casein can bind to medications, altering their absorption in the gastrointestinal tract. The fat content in milk plays a dual role, enhancing the absorption of lipophilic drugs like griseofulvin while potentially delaying the absorption of hydrophilic drugs. Milk also acts as a buffer, raising gastric pH and thereby impairing the dissolution of acid-dependent drugs. While most interactions are pharmacokinetic, some pharmacodynamic effects are notable, such as the risk of a hypertensive crisis when patients on monoamine oxidase inhibitors (MAOIs) consume tyramine-rich aged cheeses. The clinical implications are significant, especially for vulnerable populations like children and the elderly who frequently consume milk and take medications. To avoid therapeutic failure or toxicity, healthcare providers should offer personalized dietary advice. A common recommendation is to separate drug administration from milk consumption by at least one to two hours to ensure optimal medication effectiveness and safety.

1. INTRODUCTION

Milk is consumed worldwide for its nutritional value, with dairy intake averaging hundreds of pounds per person annually. Oral drug absorption is a multifaceted process governed by drug physicochemical properties, gastrointestinal physiology, and the composition of co-ingested substances, among which milk and dairy products are predominant due to their widespread dietary use. Milk presents a complex matrix of proteins, divalent cations (notably calcium and magnesium), and buffering capacity, each of which can interact with drugs (Boyd et al., 2018; Vegarud et al., 2000).

The ubiquitous consumption of milk and dairy products makes their potential interaction with orally administered drugs a significant, high-prevalence concern in clinical pharmacotherapy, potentially

compromising therapeutic outcomes through alterations in drug absorption and bioavailability (Pandey & Kumar, 2022; Subkisha et al., 2024). The clinical implications of milk-drug interactions extend across multiple therapeutic classes, necessitating careful consideration in medication management and patient counselling. Understanding the physicochemical principles governing milk-drug interactions, including pH partitioning, lipid solubility, and protein binding characteristics, is essential for predicting and preventing clinically significant interactions that could compromise patient care. This review summarizes current evidence on the pharmacokinetic and pharmacodynamic aspects of milk-drug interactions, with the goal of systematically examining their underlying mechanisms, emphasizing clinical implications, and offering recommendations to reduce risks while improving therapeutic outcomes.

2. METHODOLOGY

This paper was conducted as a scoping and narrative review to systematically synthesize the current evidence regarding the clinical pharmacology of milk-drug interactions, emphasizing underlying mechanisms, clinical implications, and therapeutic recommendations.

2.1. Search Strategy and Selection Criteria

A comprehensive search of the literature was performed across major academic databases, including PubMed/MEDLINE, Scopus, and Google Scholar. The primary search terms and keyword combinations used were: "Milk-drug interactions," "Drug-food interactions," "Pharmacokinetics," "Dairy," "Chelation," "Tetracyclines," "Fluoroquinolones," "Levothyroxine," and "Bisphosphonates". The literature search included articles published up to November 2025.

2.2. Data Inclusion and Synthesis

The review included clinical trials, systematic reviews, meta-analyses, and relevant *in vitro/in vivo* mechanistic studies that specifically addressed the interaction between milk or dairy products and orally administered drugs. The focus was on studies detailing changes in pharmacokinetic parameters (e.g., absorption, bioavailability, C_{max}, AUC) or clinically significant pharmacodynamic outcomes (e.g., therapeutic failure, toxicity). Non-peer-reviewed articles, case reports lacking pharmacokinetic data, and studies solely focusing on drug transfer into breast milk (a separate pathway) were generally excluded. Data were synthesized narratively and comparatively, with an emphasis on evaluating the magnitude of the interaction (e.g., 10% vs. 60% reduction) and assessing the strength of clinical evidence to support current therapeutic recommendations.

3. MECHANISMS OF INTERACTION

Milk is a complex emulsion containing calcium, proteins, fatty acids, lactose (milk sugar), and other micronutrients (Lambrini et al., 2021). Each component can influence drug absorption through distinct mechanisms (Figure 1).

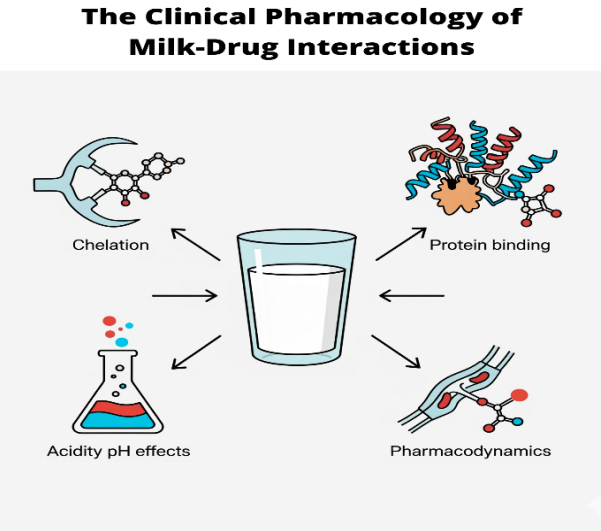

Figure 1: Key pharmacokinetic and pharmacodynamic mechanisms of milk-drug interactions.

3.1. Chelation by Calcium and Minerals

Dairy is rich in calcium (approximately 300 mg per cup of milk) and also contains magnesium and other cations. Many medications can form insoluble complexes with divalent or trivalent ions. Classic examples are the tetracycline antibiotics and fluoroquinolones – these drugs have functional groups (e.g. β-diketone in tetracyclines) that strongly bind Ca^{2+} and Mg^{2+} (Neuvonen, 1976; Walden et al., 2021). The resulting chelate complexes precipitate in the gastrointestinal tract and cannot be absorbed. Chelation is perhaps the most critical mechanism, affecting numerous drug classes.

3.2. Protein Binding and Complex Formation

Milk proteins (casein and whey) can interact with drugs physically or chemically. In the acidic stomach, casein precipitates (forming curds), which may trap drugs or bind them. Some drugs may adsorb onto these protein clumps, delaying their release or transit (Kim et al., 2018). For example, casein has been reported to reduce ciprofloxacin absorption by binding the drug in addition to the calcium effect (Pápai et al.,

2010). Furthermore, proteins can buffer stomach pH (as they have acid/base groups), potentially altering the drug's dissolution profile. While protein binding from milk is less quantifiable than calcium chelation, it likely contributes to the overall reduction in absorption for protein-bound medications (Auestad & Layman, 2021). Conversely, from a formulation perspective, milk proteins might also be used to enhance the delivery of certain compounds (e.g., encapsulating a drug to protect it through the stomach), although this is not common in typical dietary scenarios.

3.3. Fat Content and Solubilisation

Whole milk contains ~3–4% fat, primarily as triglycerides (Khan et al., 2019). During digestion, these fats are emulsified and broken down into fatty acids and monoglycerides, which can facilitate the dissolution of lipophilic (fat-soluble) drugs. Thus, milk can act as a lipid-based drug delivery system for poorly water-soluble drugs. Research has shown that some drugs have higher solubility in milk than in aqueous media, leading to increased absorption (Boyd et al., 2018; Charkoftaki et al., 2010; Dhore et al., 2017; Macheras et al., 1989; Sanka et al., 2014; Sonar et al., 2015). For instance, the antimalarial drug halofantrine (a highly lipophilic compound) remained in a crystalline suspension in milk initially, but as the milk fat underwent lipolysis in the gut, the drug was solubilized and became more bioavailable (Boyd et al., 2018). In a piglet model, administering the antibiotic clofazimine in milk boosted its oral bioavailability to ~175% compared to a non-milk vehicle (Ponsonby-Thomas et al., 2024). These findings highlight that milk's fat and emulsifying properties can enhance the absorption of certain BCS class II drugs (poor solubility, high permeability). However, this beneficial effect is drug-specific – it tends to apply to highly lipophilic drugs (like some antifungals, anti-parasitics, or vitamins) that dissolve better with fats. On the other hand, fats in milk also slow gastric emptying (as any high-caloric/fat meal does), which can delay the rate of absorption for most drugs (Song et al., 2011). A slower absorption rate (lower Cmax, delayed Tmax) might or might not be clinically significant depending on the drug's therapeutic window (Wiesner et al., 2024b). In summary, milk fat can either help or hinder drug absorption: enhancing the extent of absorption for lipophiles while delaying kinetics for others.

3.4. pH and Gastrointestinal Environment

Milk has a near-neutral to slightly acidic pH (around 6.7) and notable buffering capacity. In the stomach, ingestion of milk can raise the gastric pH temporarily (proteins in milk buffer acid, and calcium can act as an antacid initially) (Al-Behaisi et al., 2002). This change in pH can impact drugs that require a strongly acidic environment to dissolve. A prime example is ketoconazole, an antifungal that needs low gastric pH for absorption; consuming milk or other alkali foods could reduce its dissolution and bioavailability, much like taking an antacid would (Cooper et al., 2003; Sinawe & Casadesus, 2023). Conversely, milk might protect acid-labile drugs (like certain penicillins or didanosine) from degradation in the stomach by slightly neutralizing pH, though such benefits are less documented (Abuhelwa et al., 2017). Once milk reaches the small intestine, its lactose and proteins can ferment or be digested, which might alter local pH and osmolarity (Matar et al., 1996; Walters et al., 2024). Individuals with lactose intolerance cannot fully digest lactose; as a result, lactose ferments in the colon producing lactic acid and gas, potentially speeding up intestinal transit (diarrhoea). If a lactose-intolerant patient takes a drug with milk, the faster transit and altered gut environment could reduce the time for absorption, compounding the interaction (Misselwitz et al., 2019). While not a direct chemical interaction, this physiologic effect is important in subsets of patients and can be considered a pharmacokinetic interaction (reduced absorption window due to dairy-induced GI upset) (Xue et al., 2020).

3.5. Alteration of Drug Transport and Metabolism

Milk components might indirectly influence drug transporters or metabolic enzymes. For example, high calcium levels can down-regulate the absorption of iron by competition; similarly, one might speculate that calcium could compete at cation transport sites for certain drugs, though concrete examples are few (Lynch, 2000). There is no strong evidence that milk inhibits or induces CYP450 enzymes (unlike grapefruit juice's well-known effect) (Chen et al., 2018), so metabolic interactions are minimal in that regard. However, dairy can impact bile release (fat in a meal stimulates bile), which in turn affects drug solubilisation (Pavlović et al., 2018). Another aspect is that calcium can sometimes precipitate bile acids and certain drugs in the gut. For instance, calcium may bind to drugs like levothyroxine forming less absorbable complexes (Liu et al., 2023). Additionally, changes in gut motility from a heavy dairy meal could influence how quickly a drug moves past its prime absorption site (Stacher et al., 1991).

3.6. Pharmacodynamic Interactions

Although the focus is on absorption (pharmacokinetics), it's worth noting direct pharmacodynamic interactions where a component of dairy affects the drug's effect. The classic example is the "cheese effect" with monoamine oxidase inhibitors (MAOIs). Aged cheeses (a dairy product) are high in tyramine, a naturally occurring monoamine. MAOIs prevent tyramine breakdown; high tyramine intake can cause excessive release of norepinephrine, leading to dangerous hypertension (Berry, 2004; D'andrea et al., 2003; Gainetdinov et al., 2018; Gillman, 2018; Krishnan, 2007; Salter & Kenney, 2018; Varounis et al., 2017). This is not about absorption per se (tyramine is absorbed fine, but its pharmacologic effect is enhanced in the presence of MAOIs), yet it underscores that dairy products can influence drug effects beyond just uptake.

In aggregate, these mechanisms illustrate that the presence of milk in the GI tract changes the fate of many medications. The exact effect depends on the physicochemical properties of the drug (e.g., tendency to bind calcium, lipophilicity, pH solubility profile) and the composition of the dairy product (e.g., milk vs. cheese vs. yogurt – each has different fat/protein content and consistency).

4. CLINICAL IMPLICATIONS

Understanding milk–drug interactions is crucial for optimizing therapeutic outcomes. Clinically, such interactions can lead to reduced efficacy, treatment failure, or adverse effects if not managed. Below, we analyse the implications for various scenarios and populations and provide practical guidance.

4.1. Impact on Therapeutic Efficacy

When milk significantly reduces a drug's bioavailability, patients may not achieve therapeutic drug concentrations. For instance, patients on antibiotics like tetracyclines or fluoroquinolones who take their doses with dairy could experience persistent infection or delayed recovery because the drug levels in plasma and tissues are too low to effectively kill bacteria (Eljaaly et al., 2021; Leyden, 1985). A classic teaching example is a urinary tract infection not improving on oral ciprofloxacin because the patient was taking each dose with a glass of milk – the dairy calcium bound the drug, leading to less absorption and potentially sub-therapeutic levels (Neuvonen et al., 1991). Similarly, improper intake of tetracycline-class antibiotics with dairy has been linked to acne or respiratory infections not responding until the diet interaction was corrected. In the case of levothyroxine (thyroid hormone), concurrent milk ingestion lowered the drug's absorption (about 8% lower AUC in one study) (Chon et al., 2018), which could translate into inadequately treated hypothyroidism if routinely taken together. Indeed, some patients have shown elevated TSH (thyroid-stimulating hormone) levels due to taking their thyroid medication with breakfast (including milk) – a sign that the dose wasn't fully absorbed (Virili et al., 2018). These examples highlight therapeutic failures that can occur if milk–drug interactions are not accounted for. On the other hand, there are drugs where milk improves efficacy – for instance, fat-dependent drugs like certain antiparasitics may work better with milk (as seen with halofantrine or clofazimine models) (Boyd et al., 2018; Ponsonby-Thomas et al., 2024).

4.2. Influence on Safety and Side Effects

Co-ingesting milk with medication can sometimes be beneficial for safety/tolerability, even if it alters pharmacokinetics. A common clinical practice is advising patients to take irritating medications with food or milk to protect the stomach. For example, NSAIDs (like ibuprofen) are often taken with milk or a snack to reduce the risk of gastritis (Lee et al., 2022). While milk might slightly delay NSAID absorption, this is usually not problematic; the priority is preventing gastric ulceration (a pharmacodynamic benefit) (Ruiz-Hurtado et al., 2021). Another example is doxycycline, known to cause esophagitis if taken on an empty stomach. Guidance allows taking doxycycline with food or milk if needed to avoid severe GI upset. Studies indicate that although milk can lower doxycycline's peak concentration (e.g. ~20% lower C_max), the clinical efficacy may not be compromised significantly, especially for acne treatment, and the improved patient adherence (due to less nausea) is a net positive (Tao et al., 2023). Thus, the risk–benefit must be considered. If a drug has a narrow therapeutic index or is treating a serious condition, avoiding milk might be critical. If a drug's absorption is only moderately affected and it's taken for a non-life-threatening condition, allowing milk to improve comfort could be reasonable.

4.3. Special Populations

Certain groups merit extra attention regarding milk–drug interactions.

4.3.1. Pediatrics

Children often consume more dairy (milk is a major part of many children's diets) and may even take medications with milk to mask taste. Pediatric formulations (antibiotic suspensions, etc.) might be

given in a spoonful of yogurt or milk. This is problematic for drugs like oral iron supplements (iron drops mixed in milk will have reduced iron absorption due to calcium competition) or antibiotics like cefdinir (an oral cephalosporin that can form non-absorbed complexes with iron and possibly with calcium as well) (Wiesner et al., 2024a). Infants on formula (which is essentially a milk substitute fortified with minerals) may have interactions: for instance, giving oral ranitidine or phenobarbital mixed in formula might alter drug absorption kinetics in neonates (though limited data exist, it's plausible by the same mechanisms) (Pressler et al., 2023). Children are also often fast metabolizers and have different gastric pH (neonates have higher gastric pH), which can exacerbate or mitigate these interactions (Nicolas et al., 2017). Additionally, pediatric patients might not communicate subtle decreases in drug effectiveness, so caregivers and clinicians need to proactively manage dairy intake around medication schedules.

4.3.2. Geriatrics

Elderly patients frequently take multiple medications (polypharmacy) and also often consume dairy for calcium and nutrition. They may be on osteoporosis medications (bisphosphonates like alendronate) where strict dosing rules apply – these drugs have such poor absorption that any co-ingestion (even water with minerals, or coffee) drastically lowers bioavailability (Gertz et al., 1995; Wilkins Parker & Preuss, 2023). For example, alendronate taken with coffee or juice can cut absorption by 60%, and with milk nearly abolishes it (Gertz et al., 1995). Thus, older patients must be educated to take their weekly bisphosphonate fasting with plain water only. Another consideration is that older adults might have achlorhydria (lower stomach acid) or slower gastric emptying, which can interact with the effects of milk (Aalaei et al., 2021) – e.g. an elderly person with low stomach acid might already have trouble absorbing vitamin B12 or certain antifungals; milk raising pH further could worsen that. Cognitive factors are important too: if an older patient is accustomed to taking pills with their morning porridge and milk, they may forget to separate them, requiring simpler regimen adjustments or caregiver help (Austin et al., 2017; Cho et al., 2018; Smith et al., 2017). Moreover, many elderly are on thyroid replacement (Zamfirescu & Carlson, 2011), antihypertensives, or digitalis – drugs for which anecdotal interactions with milk are noted. For instance, the beta-blocker propranolol and the cardiac glycoside digoxin are mentioned as having reduced bioavailability with milk (Reis & Joaquim, 2015), so in an older patient with heart conditions, taking these with a milk-based supplement could affect blood pressure or heart rate control.

4.3.3. Pregnant and Lactating Individuals

Pregnancy often increases dairy consumption for calcium needs, but pregnant women may also be on medications (e.g., levothyroxine for gestational hypothyroidism, or iron and calcium supplements). The timing of supplements is crucial: obstetric guidelines advise separating calcium and iron to maximize iron absorption; similarly, levothyroxine should be taken on an empty stomach, separate from prenatal vitamins or dairy (Virili et al., 2018). A pregnant patient who takes her thyroid pill with a morning latte could unknowingly undermine her thyroid therapy, which is risky for fetal development. On the flip side, overly strict avoidance of dairy around medication times could contribute to calcium deficiency in pregnancy (Gil & Ortega, 2019; Huang et al., 2022). This balancing act was highlighted in a recent commentary: Australian clinicians noticed women avoiding dairy for two hours after thyroid medication, leading to concerns about inadequate calcium intake (Virili et al., 2018). They ultimately recommended that after the standard 30-60 minute post-thyroid-medication window, pregnant patients should consume their needed dairy, as evidence did not show significant interaction beyond that window (Chon et al., 2018; Thyroid Disease in Pregnancy, 2020; Wiesner et al., 2021). In lactating women, a different perspective arises: medication taken by the mother could transfer into breast milk and then to the infant (which is a separate pharmacokinetic pathway than what we discuss here). However, one should note that if a lactating mother's medication absorption is compromised by dairy, that could also indirectly affect how much of the drug gets into her milk. Generally, though, the primary concern in pregnancy and lactation is ensuring both mother and baby get adequate nutrients while medications remain effective – thus requiring careful scheduling and possibly more monitoring (e.g., checking thyroid levels, antibiotic responses, etc., more frequently if dairy co-ingestion is unavoidable).

5. RESEARCH FINDINGS

Research into milk and drug interactions has been ongoing for over half a century, ranging from *in vitro* experiments to clinical pharmacokinetic trials to meta-analyses. Here we summarize key studies and compare findings across drug classes (Table 1).

Table 1: Summary of Key Milk-Drug Interactions and Clinical Recommendations

Drug Class	Specific Drug(s)	Mechanism of Interaction	Clinical Effect	Clinical Recommendation	Reference
Antibiotics (Tetracyclines)	Tetracycline, Doxycycline	Chelation with calcium	Significantly reduced absorption (e.g., ~65% for tetracycline)	Separate administration from dairy by at least 1-2 hours.	Wiesner et al., 2024
Antibiotics (Fluoroquinolones)	Ciprofloxacin	Chelation with calcium	Reduced bioavailability (e.g., ~30% for ciprofloxacin)	Avoid concurrent consumption with dairy.	Neuvonen et al., 1991
Bisphosphonates	Alendronate, Risedronate	Chelation with calcium	Absorption is "nearly abolished"	Take with plain water only, on a completely empty stomach.	Zielińska et al., 2022; Mitchell et al., 1999
Thyroid Hormones	Levothyroxine	Chelation/complex formation with calcium	Modestly reduced absorption (e.g., ~8%)	Separate the dose from milk by at least 30-60 minutes.	Chon et al., 2018
MAOIs	Tranylcypromine, Phenelzine	Pharmacodynamic (Tyramine)	Hypertensive crisis (from tyramine in aged cheese)	Avoid tyramine-rich dairy products (e.g., aged cheeses).	Berry, 2004
Lipophilic Drugs	Griseofulvin, Halofantrine	Increased solubilization from milk fat	Enhanced bioavailability	It may be beneficial to take with milk or a high-fat meal (if prescribed).	Boyd et al., 2018
NSAIDs	Ibuprofen	Gastric irritation	(No significant PK interaction)	Often taken with milk to reduce gastric upset and improve tolerability.	Lee et al., 2022

5.1. Antibiotics (Tetracyclines and Macrolides)

One of the earliest recognized interactions was between tetracycline antibiotics and dairy. A landmark clinical trial in 1985 quantified this: J.J. Leyden and colleagues gave volunteers tetracycline or minocycline with water, food, milk, or iron. Tetracycline's bioavailability dropped 46% with food and a striking 65% with milk. Minocycline, a newer tetracycline derivative, was less affected (13% reduction with food, 27% with milk) (Leyden, 1985). This showed that not all drugs in a class behave identically – minocycline and doxycycline have higher lipid solubility and are absorbed more completely, so a glass of milk, while still reducing absorption, does not nullify their uptake to the same extent as tetracycline. Consistently, *in vitro* studies found that doxycycline binds calcium less avidly than tetracycline (Tao et al., 2023). Another tetracycline, demeclocycline, was reported to have >40% reduction with milk (Wiesner et al., 2024c). Meanwhile, macrolide antibiotics (like erythromycin, azithromycin) are less discussed in terms of dairy; they don't chelate metals, but food in general can affect their absorption. Erythromycin's acid-sensitive formulations might actually benefit from a slight pH buffer by milk (though generally it's taken on empty stomach for best absorption). A systematic review went beyond tetracyclines to examine β-lactam antibiotics and food/dairy interactions (Wiesner et al., 2024a). They found that out of 25 β-lactams studied, 18 had clinically important food interactions. With respect to milk as a beverage, they noted >40% decreases in absorption for penicillin V, penicillin G, cefalexin, and cefradine when taken with milk (Wiesner et al., 2024a). Interestingly, one cephalosporin – cefuroxime – had moderately increased absorption with milk (Wiesner et al., 2024a). Cefuroxime axetil is a prodrug that needs esterase in the gut and is known to absorb better with food (probably due to bile stimulation or solubilization), which likely explains this anomaly. This underscores

that while the general rule is "milk reduces antibiotic absorption," there are exceptions where milk or food can enhance absorption of certain drugs (especially prodrugs or those requiring lipids). The review also pointed out a lack of interaction for some antibiotics with other beverages like cranberry juice (Wiesner et al., 2024a), highlighting that the type of food/beverage matters. Overall, consistent findings are that tetracyclines and many β-lactams are negatively affected by dairy, whereas some specific agents have neutral or positive interactions.

5.2. Fluoroquinolone Antibiotics

A significant body of research in the late 1980s and early 1990s delineated the impact of dairy on quinolone antibiotics. P.J. Neuvonen published a 1991 study examining ciprofloxacin with milk and yogurt. In this crossover trial with volunteers, milk reduced ciprofloxacin's Cmax by 36% and AUC by ~30%, and yogurt caused a similar reduction (~30-36% AUC) (Neuvonen et al., 1991). The recommendation was clear: avoid taking ciprofloxacin with dairy to prevent therapeutic failure. A follow-up study in 1992 by Kivistö et al. showed that milk also significantly inhibited norfloxacin absorption. A recent systematic review and meta-analysis (*Clinical Pharmacokinetics*, 2024) compiled results for various quinolones with dietary factors. It confirmed that milk and yogurt consistently reduced the absorption of several quinolones, including ciprofloxacin, norfloxacin, pazufloxacin, and prulifloxacin, aligning with the effect of equivalent calcium supplements. However, the same review found that some fluoroquinolones (like moxifloxacin, ofloxacin, lomefloxacin, enoxacin) showed neutral interactions with dairy. Moxifloxacin, for example, is known to have minimal interaction with food or divalent cations in comparison to ciprofloxacin. These discrepancies are likely due to differences in molecular structure and binding affinity for cations. The review's general conclusion was that if a quinolone has an interaction with calcium pills, it will behave similarly with milk or yogurt (Wiesner et al., 2024b). A meta-analysis within that study might have quantified an average reduction in AUC or C_max across studies – often the decrease is on the order of 20-40%, which can be clinically significant for serious infections (Neuvonen, 1976). Importantly, regulatory documents (Summary of Product Characteristics) for fluoroquinolones have long listed dairy as a contraindicated co-administration. The consistency of findings across decades solidifies the advice that all patients on oral fluoroquinolones should separate those doses from dairy to ensure effective antibiotic exposure.

5.3. Bisphosphonates and Osteoporosis Drugs

Oral bisphosphonates (alendronate, risedronate, ibandronate) are notoriously difficult to absorb – even under optimal conditions, bioavailability is <1%. Research in the 1990s and 2000s demonstrated that any co-ingested material, especially those with calcium, virtually abolishes absorption. A 2000s study on risedronate confirmed that taking it with food (even 2 hours after a meal) significantly impaired absorption, whereas fasting gave the best results (Mitchell et al., 1999). Mechanistic studies have shown that bisphosphonates chelate calcium strongly, forming insoluble complexes, which is why milk (rich in Ca^2+) is particularly problematic (Zielińska et al., 2022). One analysis noted that a dose of alendronate with coffee or orange juice reduced absorption by ~60%, and co-ingestion with milk would be expected to be even worse. By the early 2000s, drug labels explicitly instructed patients to avoid all food and drink besides plain water with these drugs (Gertz et al., 1995). A recent open-access study in 2022 by Zielinska et al. explored food binding affinities to bisphosphonates in simulated digestion. They confirmed that calcium-containing products caused insoluble chelate formation with alendronate, further dropping its already low bioavailability (Zielińska et al., 2022). They interestingly screened various foods to see which bind bisphosphonates least – finding that egg whites and white bread bound them minimally, whereas dairy was not suitable (Ichikawa et al., 2025; Zielińska et al., 2022). This line of research suggests potential for "safe foods" vs "unsafe foods" when timing cannot be perfectly empty stomach (though current clinical practice remains to administer bisphosphonates in a completely fasted state). In summary, the research consensus is unwavering: bisphosphonates should never be taken concurrently with dairy. The interactions are consistently adverse, and even a small amount of milk can reduce an already tiny absorbed fraction to nearly zero. This can have grave implications for bone density outcomes if patients are not truly getting the medication.

5.4. Other Notable Drug Classes and Examples

5.4.1. Thyroid Hormone (Levothyroxine)

As discussed earlier, a 2018 study by Chon et al. demonstrated reduced levothyroxine absorption with milk. This was a controlled pharmacokinetic study on healthy volunteers, showing about an 8% decrease in total T4 absorption over 6 hours when taken with

355mL skim milk. While modest, this effect could be clinically relevant in patients who require precise dosing. Prior to this study, it was *assumed* milk interfered because calcium supplements do (calcium carbonate taken with levothyroxine can cause elevations in TSH). Chon's study provided direct evidence, leading to reinforced counselling for thyroid patients (Chon et al., 2018). However, as the RACGP article in 2023 noted, beyond the 30-60 minute window, there is no data – meaning if a patient waits the instructed time after the dose, moderate dairy intake thereafter likely has no significant effect (Chon et al., 2018; Thyroid Disease in Pregnancy, 2020; Wiesner et al., 2021). Some discrepancies in advice (2-hour avoidance vs. 1-hour) were identified and corrected in Australia to avoid unnecessarily long fasting that might reduce calcium intake (Ichikawa et al., 2025; Kruger et al., 2007). Thus, research on levothyroxine teaches us that even small studies can influence practice, and that we should balance evidence with nutritional needs.

5.4.2. Iron Supplements and Multivalent Ions

Although not a drug in the classical sense, iron (often taken as ferrous sulfate for anemia) has absorption heavily affected by dairy. Calcium competes with iron uptake in the gut. Decades of nutrition research show that drinking milk with iron-rich meals inhibits iron absorption. For patients on oral iron therapy, consuming milk at the same time can blunt the increase in hemoglobin. This is often relevant in pediatrics (toddlers who drink a lot of cow's milk can develop "milk anemia" partly because calcium and casein hinder iron absorption from other foods). The recommendation is to avoid giving iron supplements with milk; instead, give with vitamin C or on an empty stomach (Hallberg et al., 1992). This interaction is more nutritional than pharmacologic, but it parallels the principles we see with drugs.

5.4.3. Beta-Lactams

The interaction of beta-lactam antibiotics with milk appears to be more varied compared to tetracyclines and fluoroquinolones. Research indicates that for several beta-lactams, including ampicillin, cefaclor, cefroxadine, cefradine, cloxacillin, oxacillin, penicillin V, and sultamicillin, food intake generally has a negative impact on their absorption. Specifically, when considering milk as the beverage, the extent of absorption was found to be decreased by more than 40% for cefalexin, cefradine, penicillin G, and penicillin V. Conversely, the absorption of cefuroxime was observed to increase moderately in the presence of milk. Additionally, the bioavailability of cefdinir is significantly reduced when taken with iron salts (Wiesner et al., 2024a). These findings suggest that the interaction between beta-lactam antibiotics and milk is not uniform across the entire class. While some antibiotics in this group experience reduced absorption when taken with milk, potentially impacting their efficacy, others might have their absorption enhanced or remain largely unaffected. This variability underscores the importance of considering each specific beta-lactam antibiotic individually when assessing the potential for interaction with milk. Healthcare providers should consult specific guidelines for each drug to provide accurate advice to patients regarding their administration with or without milk.

5.4.4. Antacids, H2 Blockers, and PPIs

These aren't interactions with milk, but rather other things that change pH, similar to milk. For example, proton pump inhibitors (PPIs like omeprazole) raise gastric pH significantly, and this can reduce the absorption of drugs needing acidity (similar to milk's mild effect). Interestingly, one review listed omeprazole itself as a drug whose absorption is interfered by milk (Ogawa & Echizen, 2010). This is not a commonly cited interaction; omeprazole is enteric-coated and usually taken before meals regardless. It's possible that milk's pH change or other factors slightly alter omeprazole's dissolution. Regardless, PPIs and H2 blockers demonstrate how altering gastric pH (as milk does, albeit weakly) can have downstream impacts on drug absorption. Additionally, there is the concept of "milk-alkali syndrome," where excessive milk and antacids cause hypercalcemia and metabolic alkalosis; while not directly a drug absorption issue, it underscores that milk plus calcium-containing medications (like calcium carbonate antacids) can have systemic effects (Medarov, 2009).

5.4.5. Cardiovascular Drugs

Some surprising interactions have been noted. The secondary review by Reis (2015) lists propranolol (a beta-blocker) and amiloride (a potassium-sparing diuretic) as having reduced bioavailability with milk. Critically, primary pharmacokinetic studies confirming a major interaction for these two agents are not widely cited, suggesting these entries may stem from older, less-replicated observations. Propranolol is lipophilic and highly protein-bound; one might think milk's fat could increase its absorption, but propranolol also undergoes first-pass metabolism extensively. If milk slows absorption, it could reduce C_max but perhaps

increase AUC. Without specific data, it's hard to interpret, but clinicians haven't historically warned about milk with beta-blockers. It might have been an observation in a small study where milk slightly lowered propranolol plasma levels. As for amiloride, it's a fairly polar molecule; perhaps milk delayed its absorption, or the alkaline load of milk affected its urinary excretion. These instances highlight that more research could be needed to confirm less obvious interactions. They also remind us that when giving any drug with nutritional supplements like Ensure (which contains milk protein) or via feeding tubes with dairy formulas, checking for interactions is wise. Another cardiovascular example: digoxin (for heart failure) was noted to have a possible milk interaction (Reis & Joaquim, 2015). Digoxin absorption can be affected by many factors (e.g. fiber, gut flora). If milk reduces digoxin levels significantly, it could lead to loss of rate control or heart failure symptoms. However, current digoxin monographs don't list milk as a major concern.

5.4.6. Miscellaneous Drugs

Some other drugs mentioned in literature include mercaptopurine (an oral chemotherapy for leukemia) – dairy may reduce its bioavailability (Reis & Joaquim, 2015), which is crucial since dosing is weight-based and precise for remission maintenance. Patients (often children) on mercaptopurine are typically counseled to avoid milk around the dose. Lithium was referenced in a functional medicine article as interacting with dairy (Eljaaly et al., 2021). Lithium absorption isn't known to be decreased by milk significantly (it's a small ion that is readily absorbed), but lithium's excretion is sensitive to sodium – not directly a dairy issue unless large volumes of milk (with sodium/calcium) alter renal handling. Possibly they included lithium because of reports that calcium might affect its levels, or simply to reinforce separating it from any cation-rich food. In any case, the evidence is not strong, indicating a need for more clarity. Another example is antiretroviral drugs for HIV: integrase inhibitors such as dolutegravir and elvitegravir can chelate with polyvalent cations similar to quinolone antibiotics (Podany et al., 2016). Product guidelines for dolutegravir state if taken without food, it should be separated by a few hours from calcium-rich foods or supplements (Waters et al., 2022). A study found that taking dolutegravir together with a calcium-fortified meal did not significantly diminish levels (because food slows its absorption, allowing time to avoid chelation), whereas taking the pill with just milk on an empty stomach would likely reduce absorption (Song et al., 2014). This nuance (meal-dependent effect) was illustrated in a BHIVA (British HIV Association) document (Waters et al., 2022). It emphasizes that for medications like these, instructions can be complex: patients are told either to take with a full meal if they're having dairy, or if they prefer to take on an empty stomach, to avoid dairy around it.

Beyond the aforementioned drug classes, other medications have also been reported to interact with milk. Lithium, a medication used to treat bipolar disorder, can potentially have its effects influenced by high calcium intake from dairy, as long-term lithium use can sometimes lead to an increase in calcium levels in the body (Steardo et al., 2020). Some HIV medications, such as dolutegravir, may experience reduced absorption if taken concurrently with calcium-rich dairy products, unless they are consumed as part of a meal (Podany et al., 2016). Methotrexate, an immunosuppressant and antimetabolite, may have its levels decreased when taken with milk-rich foods (Koziolek et al., 2019). Interestingly, not all interactions with milk result in decreased absorption. For instance, one study found that the absorption of enoxacin, an antibiotic, was not impaired by milk intake (Lehto & Kivistö, 1995). Furthermore, research suggests that milk digestion is crucial for the solubilization and absorption of halofantrine, an antimalarial drug, indicating a potential benefit of taking this medication with milk (Boyd et al., 2018). Similarly, the absorption of cefuroxime, a beta-lactam antibiotic, has been observed to increase moderately with milk consumption (Wiesner et al., 2024a). These diverse interactions highlight the importance of considering the specific properties of each drug when evaluating the potential for interaction with milk.

5.5. Consistent Findings vs. Discrepancies

Across the literature, some patterns are very consistent: calcium-mediated chelation causing decreased absorption is well-documented for antibiotics (tetracyclines, fluoroquinolones), bisphosphonates, thyroid hormone, and iron. The magnitude can range from moderate (~10-30% reductions, as with doxycycline or levothyroxine) to severe (>50% reduction, as with tetracycline, certain cephalosporins, and alendronate) (Leyden, 1985; Wiesner et al., 2024a). These consistent findings have made it into standard prescribing guidelines and patient counseling points. On the other hand, discrepancies exist in less-studied drugs and in newer agents. For example, one cephalosporin (cefuroxime) bucking the trend with increased absorption on a full stomach with milk (Wiesner et al., 2024a), or the case of minocycline being less affected by milk than older

tetracyclines (Leyden, 1985), or moxifloxacin having negligible interaction while ciprofloxacin is heavily affected (Reis & Joaquim, 2015). These discrepancies often relate to a drug's chemistry – e.g., moxifloxacin doesn't chelate as strongly, cefuroxime axetil is a prodrug needing esterase, which are more active post-meal. Another area of discrepancy is the clinical significance of the interactions. Some studies note a pharmacokinetic change but conclude it's not clinically meaningful. For instance, a slight reduction in AUC for a drug with a wide therapeutic window might not change patient outcomes. We saw this debate with levothyroxine: a statistically significant drop in T4 levels was observed (Chon et al., 2018), yet whether that affects a patient's TSH enough to matter is debatable. In contrast, for an antibiotic treating a serious infection, even a 20% reduction could be critical if the pathogen is only marginally susceptible (Ruiz-Ramos et al., 2023).

6. REGULATORY GUIDELINES AND RECOMMENDATIONS

Regulatory bodies issue guidelines concerning food-drug interactions, which include specific recommendations regarding the consumption of milk with certain medications (Lynch, 2000). Many drug labels for medications known to interact with milk contain explicit warnings and instructions about the timing of administration relative to dairy intake (Tao et al., 2023). These recommendations typically advise patients to separate the administration of the drug from the consumption of milk or other dairy products by a specified time interval, often ranging from 1 to 4 hours (Zergiebel et al., 2022). Certain guidelines are tailored to specific drug classes; for example, the recommendation to take bisphosphonates with plain water on an empty stomach and to avoid dairy for a defined period afterward is a well-established guideline (Song et al., 2014). However, inconsistencies in labeling and recommendations can sometimes occur, as illustrated by the varying advice surrounding the interaction between doxycycline and milk (Martínez et al., 2024). While regulatory guidelines provide a crucial framework for managing these interactions, ensuring their consistent application and promoting patient understanding remain ongoing challenges. Healthcare professionals play a vital role in providing clear, accurate, and up-to-date instructions to patients regarding potential milk-drug interactions.

7. CONCLUSION

Milk and dairy products significantly influence drug therapy, often in under-recognized ways. Pharmacokinetic interactions primarily involve calcium-induced chelation that reduces absorption of drugs like tetracyclines, fluoroquinolones, bisphosphonates, levothyroxine, and iron supplements, as well as changes in solubility and gastric emptying that may hinder or sometimes enhance absorption. Pharmacodynamic effects, such as tyramine in aged cheese provoking hypertensive crises with monoamine oxidase inhibitors (MAOIs), highlight that not all interactions occur via absorption.

Clinically, these interactions can lead to treatment failure, persistent infection, hormonal imbalance, or increased fracture risk. Preventive strategies are simple yet vital: separating drug and dairy intake, educating patients—especially children, pregnant women, and the elderly—and monitoring therapy when avoidance is impossible. For providers, this means routinely inquiring about dietary habits, counselling on appropriate timing (e.g., 30 minutes for levothyroxine vs. longer or strict avoidance for fluoroquinolones and bisphosphonates), and considering alternatives when needed.

Evidence consistently shows significant reductions in antibiotic and osteoporosis drug absorption, while variable effects with newer agents warrant further research. Ultimately, milk–drug interactions exemplify the vital link between diet and pharmacotherapy, underscoring that safe, effective treatment requires aligning nutrition with medication use.

7.1 Limitations and Future Directions

This review is limited by its primary focus on oral drug absorption and the scope of the literature search. While many older and high-impact drug-dairy interactions are well-documented, data are limited for many newer drug classes, particularly in specialized areas like oncology and HIV. The clinical significance of small pharmacokinetic changes, such as the 8% reduction observed for levothyroxine, remains debatable, necessitating a balance between therapeutic efficacy and maintaining adequate nutritional intake, especially in vulnerable populations.

Future research could further explore the nuanced roles of specific milk proteins in drug interactions, investigate the impact of different types of milk (e.g., skim, whole, fortified, plant-based alternatives) on drug absorption, and examine the prevalence and clinical outcomes of milk-drug interactions across diverse populations. A continued focus on understanding and managing these interactions is essential to optimize pharmacotherapy and ensure patient safety.

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Conflict of interest

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